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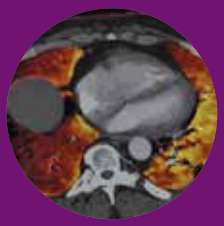

Cleveland Clinic

RespiratoryExchange

Research and News for Physicians from Cleveland Clinic's Respiratory Institute

Winter | 2016

FEATURE

Probe-Based Confocal Light Endomicroscopy and the Optical Biopsy

– P. 10

Dear Colleagues:

Welcome to this issue of *Respiratory Exchange*, which offers a look inside some of the latest clinical innovations, emerging research and new treatment modalities within Cleveland Clinic's Respiratory Institute.

Among the highlights in this issue are:

- Further information on the role of the mechanosensitive ion channel, TRPV4, in infection-associated acute respiratory distress syndrome (ARDS). This expands upon our cover story report in last year's *Respiratory Exchange*.
- The addition of probe-based confocal light endomicroscopy to optical biopsies to diagnose acute cellular rejection, and whether this can replace risky transbronchial biopsies in high-risk patients.
- The role of novel imaging techniques — such as single photon emission computed tomography ventilation perfusion scintigraphy and dual energy CT scan — to assess pulmonary perfusion, as well as emerging therapeutic options such as balloon pulmonary angioplasty.
- Ongoing research projects are defining the impact of expansion of recipient and donor selection criteria on lung transplant outcomes and alternative lung allocation models to improve patient access, outcomes and quality of life.
- Allergy and Clinical Immunology identified antibiotics as the most common cause of perioperative anaphylaxis at Cleveland Clinic, aiding in direct patient management.
- An examination of the cost-effectiveness of bronchial thermoplasty for patients with severe asthma found therapy is most cost-effective in younger patients with high asthma exacerbation rates.
- A case study by Cleveland Clinic's Hereditary Hemorrhagic Telangiectasia Treatment (HHT) Center highlights the unique risks pregnancy poses to patients with HHT.

I hope you enjoy this issue of *Respiratory Exchange*. Inside you'll find a listing of actively enrolling clinical trials, as well as news about how the accomplishments of our pulmonary, critical care medicine, and allergy and clinical immunology staff are impacting the field. To learn more about our clinical research activities, please visit clevelandclinic.org/pulmonary.

If you have questions or would like to refer a patient, call 866.CCF.LUNG (866.223.5864). We're here to help.

Sincerely,

Herbert P. Wiedemann, MD, MBA
CHAIRMAN | CLEVELAND CLINIC RESPIRATORY INSTITUTE

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Expanding the Role of the Mechanosensitive Ion Channel, TRPV4, to Infection-Associated Acute Respiratory Distress Syndrome (ARDS): Discovery may lead to novel therapies

By Rachel G. Scheraga, MD

Our laboratory has recently shown that the mechanosensitive, calcium-permeable, plasma membrane ion channel named transient receptor potential vanilloid 4 (TRPV4) plays a role in myofibroblast differentiation and in vivo lung fibrosis[1].

THE ROLE OF MACROPHAGES

The pathogenesis of pulmonary fibrosis depends on soluble factors and a mechanical signal (extracellular lung matrix stiffness). Similarly, effective macrophage engulfment of foreign particles (phagocytosis) requires orchestration of macrophage surface receptors, the particle itself and the extracellular matrix.

Acute respiratory distress syndrome (ARDS) from an infectious stimulus is a complex process characterized by endothelial and alveolar epithelial injury followed by recruitment and accumulation of inflammatory cells (i.e., macrophages) in the injured alveolus. Macrophages play a key role in lung injury and fibrosis by producing cytokines and other inflammatory remodeling factors. Hence, we sought to determine the role of TRPV4 in clearance of infection by macrophages (phagocytosis) and associated lung tissue injury.

INVESTIGATING TRPV4

We investigated the role of TRPV4 in integrating the dual signals provided by matrix stiffness and lipopolysaccharide (LPS), an important constituent on the surface of gram-negative bacteria, to control macrophage phagocytosis and cytokine production for host defense and resolution of lung injury.

Taken together, these results implicate the mechanosensing channel, TRPV4, in the pathogenesis of gram-negative bacterial pneumonia and resolution of associated acute lung injury by integrating the LPS and the matrix stiffness signals for macrophage phagocytosis and pro-resolution cytokine release.

In work recently published in the *Journal of Immunology*, we showed that inhibition of TRPV4 by pharmacologic agents or downregulation/deletion of TRPV4 resulted in almost complete blockage of LPS-stimulated macrophage phagocytosis in vitro and in vivo in a matrix stiffness-dependent manner. Moreover, TRPV4 mediated the LPS signal to release anti-inflammatory/pro-resolution cytokines in macrophages.

RESULTS

Taken together, these results implicate the mechanosensing channel, TRPV4, in the pathogenesis of gram-negative bacterial pneumonia and resolution of associated acute lung injury by integrating the LPS and the matrix stiffness signals for macrophage phagocytosis and pro-resolution cytokine release.

Pharmacologic agents targeting TRPV4 are currently under development and in Phase I clinical trials. Successful targeting of TRPV4 channel activity may lead to therapeutic approaches to treat bacterial pneumonia and associated ARDS. ●

Dr. Scheraga is an associate staff physician in the Respiratory Institute and holds a secondary appointment in the Lerner Research Institute Department of Pathobiology. For more information, contact Dr. Scheraga at 216.444.4429 or scherar@ccf.org.

Reference

Scheraga, RG, Abraham S, Niese KA, Southern BD, Grove LM, Hite RD, McDonald C, Hamilton TA, Olman MA. 2016. TRPV4 mechanosensitive ion channel regulates lipopolysaccharide-stimulated macrophage phagocytosis. *The Journal of Immunology* 196(1): 428-36.

Investigating Novel Therapies for Scleroderma-Associated Interstitial Lung Disease

Cleveland Clinic recruiting patients for multinational trial

By Kristin Highland, MD, MS

Systemic sclerosis (SSc) is a devastating disease of unknown etiology. The pathogenesis of SSc is characterized by systemic (multiorgan) immunological, vascular and fibrotic abnormalities. Interstitial lung disease (ILD) is a leading cause of morbidity and mortality in patients with SSc, with an associated median survival of five to eight years.

As no approved SSc-ILD treatment is available, and internal organ fibrosis, especially lung fibrosis, leads to severe loss of function and ultimately results in death, there is a high unmet medical need to stop the fibrotic remodeling and thus prevent loss of organ function.

PHASE III MULTINATIONAL TRIAL

Dr. Oliver Distler of the University of Zurich and I are the coordinating investigators for the SENCIS™ trial. This is a double-blind, randomized, placebo-controlled trial evaluating efficacy and safety of oral nintedanib treatment for at least 52 weeks in patients with systemic sclerosis associated interstitial lung disease (SSc-ILD) and is sponsored by Boehringer Ingelheim. This multinational, 520-person Phase III trial is the largest scleroderma trial ever undertaken.

NINTEDANIB

Nintedanib is a small molecule that inhibits a distinct spectrum of receptor tyrosine kinases (RTKs) and nonreceptor tyrosine kinases (nRTKs), including vascular endothelial growth factor receptor, platelet-derived growth factor receptor, fibroblast growth factor receptor and SRC family kinases (Src, Lck and Lyn belonging to a family of proto-oncogene tyrosine-protein kinases). All of these growth factor pathways and their downstream signal cascades have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodeling.

In experiments with dermal fibroblasts from patients with SSc, nintedanib inhibited migration and proliferation, reduced the expression of extracellular matrix markers, and attenuated transformation to myofibroblasts. In animal models of SSc, nintedanib effectively attenuated skin and lung fibrosis, reduced extracellular matrix deposition in skin and lung, attenuated myofibroblast accumulation in skin and lung, and reduced dermal thickening. Nintedanib also reduced dermal microvascular endothelial cell apoptosis and effectively attenuated pulmonary vascular remodeling by reducing the number of vascular smooth muscle cells and occluded pulmonary vessels.

Based on preclinical and clinical evidence of antifibrotic activity of nintedanib in idiopathic pulmonary fibrosis (IPF) and preclinical evidence of potential effects in SSc, along with an acceptable safety profile as demonstrated in clinical trials with nintedanib in IPF, investigation in a patient population with active SSc-ILD accompanied by varying degrees of skin and other organ fibrosis is medically rational.

PATIENT RECRUITMENT

Cleveland Clinic is actively enrolling patients in this trial. Main inclusion criteria include:

1. Age ≥ 18 years
2. Must fulfill the 2013 ACR/EULAR classification criteria for scleroderma
3. SSc disease onset within 5 years of visit 1
4. Extent of ILD ≥ 10% on HRCT
5. FVC ≥ 40% of predicted
6. DLCO (corrected for Hb): 30% to 89% of predicted

Patients are able remain on stable background mycophenolate or methotrexate. ●

Dr. Highland is a member of the Department of Pulmonary Medicine. She can be reached at 216.445.5429 or highlak@ccf.org.

Antibiotics Are a Common Cause of Perioperative Anaphylaxis

By Lily C. Pien, MD, MHPE; Alexei Gonzalez-Estrada, MD; and David M. Lang, MD

Perioperative anaphylaxis is an acute, systemic, potentially life-threatening reaction that occurs during the operative period. Comprehensive evaluation of these cases is complicated, as patients who experience perioperative anaphylaxis routinely receive multiple pharmacologic agents simultaneously during general anesthesia. For this reason, establishing the cause of perioperative anaphylaxis is usually quite challenging.

IDENTIFYING THE CULPRIT

The differential diagnosis consists of not only medications, but also other potential etiologies, including latex allergy and systemic mast cell disorders. Identifying the etiology, or responsible agent, in a case of perioperative anaphylaxis is essential to provide direction to the surgeon and anesthesiologist so that the causative agent can be avoided in future surgical procedures.

Diagnostic evaluation using skin or in vitro tests for specific immunoglobulin E (IgE) antibodies to suspected agents is recommended, ideally four to six weeks after the event.[1] This evaluation should include all the agents administered during the procedure in addition to other possible etiologic factors (e.g., latex and chlorhexidine).

CAUSES AND PATTERNS

A recent study from Cleveland Clinic reported an incidence of perioperative anaphylaxis of one in every 4,583 procedures.[2] Previous studies found neuromuscular blocking agents were the most common identifiable cause of perioperative anaphylaxis.[3] In our Department of Allergy and Clinical Immunology, we sought to identify the patterns and causes for perioperative anaphylaxis at Cleveland Clinic.

We performed a retrospective medical record review from July 1, 2002, to Oct. 31, 2013, and identified 30 cases of perioperative anaphylaxis. The demographic characteristics of these cases were female gender (63%), Caucasian background (83%) and nonatopic status (67%), with a median age of 53.5 years.

The most frequent presenting sign of perioperative anaphylaxis was hypotension (97%); almost one in four (23%) cases presented with cardiac arrest. The majority of reactions occurred during the induction phase of anesthesia. An IgE-mediated allergen was identified in 57 percent of cases.

The most common identifiable cause for perioperative anaphylaxis was antibiotics (59%), followed by neuromuscular blocking agents (23%) and latex (18%). Among the responsible antibiotics, nine out of 10 were beta-lactam antibiotics, with the most common drug being cefazolin.

In 13 cases, no causative agent was identified. Among those cases in which serum tryptase levels were obtained, elevated tryptase was found in 10 out of 10 (100%) cases of IgE-mediated anaphylaxis, compared with four out of 10 (40%) cases without identifiable cause. No deaths were reported in the 30 cases of perioperative anaphylaxis. Twenty-one patients went on to have subsequent surgery without remarkable adverse reactions.

A CLINICAL CHALLENGE

Perioperative anaphylaxis, though rare, remains a clinical challenge and a surgical obstacle for clinicians and patients. Our study is valuable in several respects:

- We found antibiotics are more common in causing perioperative anaphylaxis in our setting, a tertiary healthcare center where more than 190,000 surgeries were performed in 2014.
- Our report that antibiotics are the most common cause for perioperative anaphylaxis[4] is supported by the findings of two recent studies conducted in the United States.[5,6]
- We isolated patient characteristics that can be helpful during the preoperative evaluation phase.

Our report illustrates the utility of performing a systematic allergy/immunology evaluation for patients who have had perioperative anaphylaxis. This evaluation can identify responsible agents to be avoided in the future, direct management when patients require future surgical procedures and lead to better outcomes for involved patients. ●

Dr. Pien is a member of the Department of Allergy and Immunology who can be reached at 216.444.6933 or pienl@ccf.org.

Dr. Gonzalez is a former fellow in the department who is now on the faculty at East Tennessee State University.

Dr. Lang is Chair of the Department of Allergy and Immunology, Co-Director of the Asthma Center and Director of the Allergy/Immunology Fellowship Training Program. He can be reached at 216.445.5810 or langd@ccf.org.

See references page 29.

Surfactant Replacement Therapy in ARDS: A Rationale for Future Optimism

By R. Duncan Hite, MD

In the United States, acute respiratory distress syndrome (ARDS) affects over 250,000 persons per year, leading to death in up to 40 percent of cases. With age as a risk factor for ARDS, patient numbers will increase as the U.S. population ages.

ARDS IMPACT

Survivors encounter prolonged ICU stays on mechanical ventilation and decreased quality of life, while substantial costs impact the individual and the healthcare system. A wide variety of common acute conditions (infection, trauma, transfusions and more) serve as triggers, contribute to the complexity and severity, and influence response to treatment approaches.

SURFACTANT REPLACEMENT THERAPY

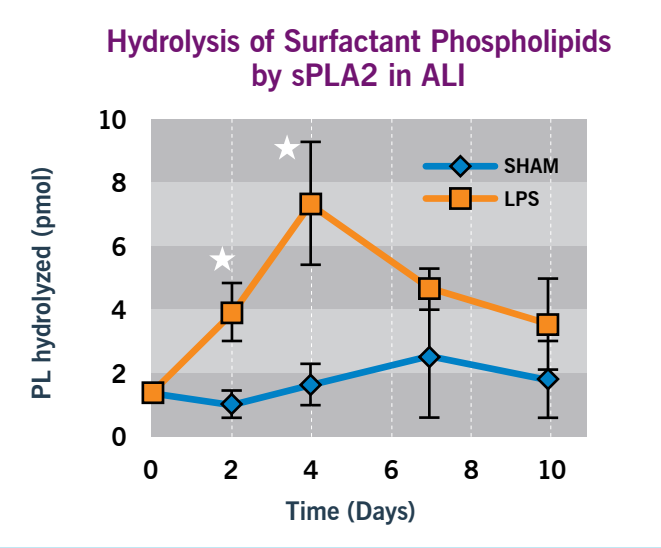
Surfactant degradation, inhibition and inactivation is a well-characterized and physiologically important contributor to the pathogenesis of ARDS. Premature newborns (born prior to 32 weeks' gestation) are at high risk of developing neonatal respiratory distress (nRDS). Over two decades, surfactant replacement therapy (SRT) became a standard component in the care of infants with nRDS, leading to dramatic reductions in infant mortality rates.

The success of SRT in nRDS led both clinicians and researchers to enthusiastically pursue the potential benefits of SRT for ARDS in adults and children. Unfortunately, multiple large multicenter clinical trials with SRT failed to demonstrate improved clinical outcomes, and dampened interest in and support for continued investigation into this therapeutic approach.

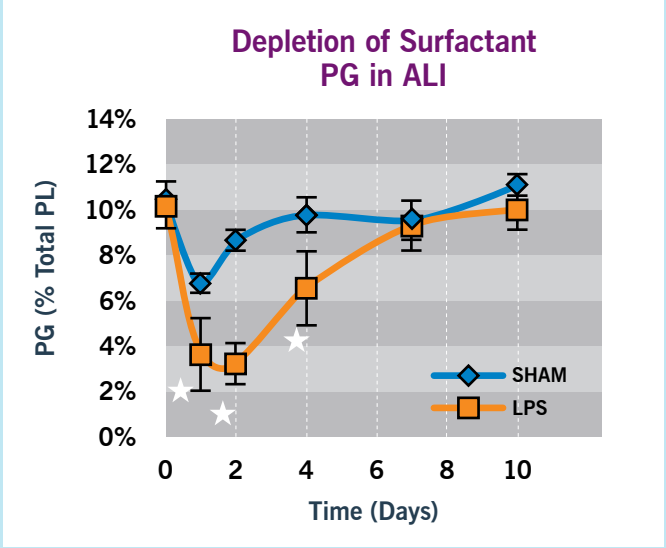
Interestingly, several SRT trials reported transient improvements in oxygenation and lung function, which were not sustained after completion of SRT. These observations very likely reflect the impact of degradation of the exogenous SRT via the same mechanisms that resulted in injury of the patient's endogenous surfactant.

ENHANCING SRT APPROACHES

Our research team demonstrated that secretory phospholipases A2 (sPLA2s)



› **Figure 1:** Secretory PLA2 activity (hydrolysis of surfactant phospholipid) increases after intratracheal LPS in mice with peak activity at day 4 and return to near normal by day 10.



› **Figure 2:** Depletion of PG in mice peaks 2 days after intratracheal LPS with full recovery by days 7-10.

Using these results, novel SRT approaches that reduce ARDS severity and accelerate ARDS resolution are being developed and will be utilized in future Phase I/II clinical trials.

hydrolyze surfactant phospholipids and serve as a potent mechanism for surfactant degradation in patients with ARDS, including early and late disease stages.[1] In particular, the Group IIA sPLA2 (PLA2G2A) isoform is increased in the BAL fluid of patients with ARDS and correlates with depletion of phosphatidylglycerol (PG), an anionic phospholipid that contributes a critically important biophysical interaction with surfactant protein B (SP-B). This work also demonstrated that PLA2G2A hydrolyzes alveolar phospholipids at both the air-liquid interface and aqueous subphase, and that hydrophobic surfactant proteins (SP-B and SP-C) protect surfactant from hydrolysis by sPLA2.[2]

These data suggest that revised approaches to SRT — that anticipate and account for the kinetics of surfactant degradation, including sPLA2 inhibition and/or uniquely designed surfactant preparations (emphasizing PG and surfactant proteins) — may provide important enhancements that improve on the results of prior clinical trials.

In pursuit of that ambition, our current efforts have focused on animal models of ARDS that can fully characterize the time course for surfactant degradation and dysfunction, including changes in PLA2G2A, PG and SP-B.[3] Using these results, novel SRT approaches that reduce ARDS severity and accelerate ARDS resolution are being developed and will be utilized in future Phase I/II clinical trials.

It is not surprising that the negative results of multicenter SRT trials led to pessimism for many. Despite those deterrents, our optimism persists due to the firm original theory behind SRT and development of novel approaches that seek to revise and refine SRT through an enhanced understanding of SRT pharmacokinetics in the setting of ARDS. ●

Dr. Hite is Chair of the Department of Critical Care Medicine in Cleveland Clinic's Respiratory Institute. He can be reached at 216.445.3099 or hited@ccf.org.

References

1. Hite RD, Grier BL, Waite BM, Veldhuizen RA, Possmayer F, Yao LJ, Seeds MC. Surfactant protein B inhibits secretory phospholipase A2 hydrolysis of surfactant phospholipids. *Am J Physiol Lung Cell Mol Physiol*. 2012 Jan;302(2):L257-L265.

2. Seeds MC, Grier BL, Suckling BN, Safta AM, Long DL, Waite BM, Morris PE, Hite RD. Secretory phospholipase A2 mediated depletion of phosphatidylglycerol in early acute respiratory distress syndrome. *Am J Med Sci*. 2012, 343, 446-51.

3. Hite RD, Chakrabarti A, Novotny MJ, Files DC, Waite MB, Seeds MC. Reduced lung compliance and phospholipase-mediated depletion of phosphatidylglycerol in a murine ARDS model. *Am J Resp Crit Care Med*. 2015, 191, A2055.

Increasing Access to Lung Transplant Through Changes in Donor Lung Allocation

By Wayne Tsuang, MD, MHS, and Maryam Valapour, MD, MPP

Lung transplantation remains the definitive treatment for end-stage lung diseases, with the number of lung transplants in the United States reaching an all-time high of 1,946 in 2013. Leading indications for transplant include pulmonary fibrosis, chronic obstructive pulmonary disease, cystic fibrosis and pulmonary hypertension. Despite the increase in the number of transplants, the number of organ donors is outpaced by the number of patients on the waiting list. Therefore, our research efforts are focused on the efficient utilization and distribution of available organs.

HOW U.S. LUNG ALLOCATION WORKS

The geographic location of an organ donor is a major criterion for allocation. Organs are first offered to nearby, or "local," wait-listed patients prior to being offered to a wider region. "Local" is defined as within the donation service area (DSA) administered by an organ procurement organization. There are 58 DSAs in the United States with boundaries that were determined in the early years of transplant mainly in light of ischemic time (Figure 1). If no wait-listed candidates within the boundaries of the DSA are identified, the donor lungs are offered beyond the local DSA in 500-mile-radius increments from the donor's location until the organ is accepted.

Another major criterion for organ distribution is donor age, which determines the priority of patient age groups eligible to receive the organs within each geographic area. Patient age groups are defined as adults ≥ 18 years of age, adolescents 12 to 17 years, and children < 12 years. Adult donor lungs are first offered to adults or adolescents, and then children, within the local area. Adolescent donors lungs are first offered to adolescents, and child donor lungs are first offered to children before the other age groups are considered (Figure 2).

Only after using the donors' geographic location and age to identify a cohort of wait-listed patients are additional clinical criteria used. These criteria include ABO blood type, thoracic size, immunologic compatibility and Lung Allocation Score (LAS). The LAS was implemented in 2005 and is a weighted score that incorporates both medical urgency (estimated survival without transplant) and transplant benefit (difference between estimated survival with and without transplant). The score ranges from 0 to 100 and the higher the score, the higher the priority for transplant. The LAS applies to adult and adolescent wait-listed patients; children on the waiting list are prioritized as status 1 or 2 depending on clinical data and time accrued on the waiting list.

Figure 1: Donation service area boundaries and lung transplant centers.

Lung Donor < 12 years		
Sequence	Geographic Zone	Candidate
1	1,000-mile radius	Child
2	500-mile radius	Adolescent
3	Local DSA	Adult
4	500-mile radius	Adult
5	1,000-mile radius	Adolescent
6	1,000-mile radius	Adult
Continue in 500-mile-radius increments, allocating to child, adolescent and then adult within each increment.		

Lung Donor 12-17 years		
Sequence	Geographic Zone	Candidate
1	Local DSA	Adolescent
2	Local DSA	Child
3	Local DSA	Adult
4	500-mile radius	Adolescent
5	500-mile radius	Child
6	500-mile radius	Adult
Sequence repeats in 500-mile increments.		

Lung Donor ≥ 18 years		
Sequence	Geographic Zone	Candidate
1	Local DSA	Adult+Adol
2	Local DSA	Child
3	500-mile radius	Adult+Adol
4	500-mile radius	Child
5	1,000-mile radius	Adult+Adol
6	1,000-mile radius	Child
Sequence repeats in 500-mile increments.		

› **Figure 2:** Current donor lung allocation algorithm with age and geography criteria.

STUDYING ALTERNATIVE ALGORITHMS FOR PEDIATRIC PATIENTS

The U.S. organ allocation systems are designed to prioritize wait-listed pediatric patients (adolescents and children) for transplant, thereby minimizing the impact of end-stage organ disease on their life span and quality of life. But does the current system for lung transplant do this adequately?

This question was raised during a recent national controversy involving an 11-year-old patient with cystic fibrosis. This patient, and a dozen other similarly aged patients who followed, were permitted to seek simultaneous access to adult, adolescent and child donors. However, this measure has not been as effective as hoped; very few wait-listed children successfully matched with an adolescent or adult donor due to thoracic size considerations.

IMPROVING ACCESS FOR PEDIATRIC PATIENTS

Ideal strategies to increase lung transplant rates for pediatric patients require improving access to pediatric donors. Recent research in liver transplant showed that broader geographic sharing of donor livers increased transplant rates for the highest acuity wait-listed patients. We applied the principles of broader geographic sharing to the pediatric lung population by modeling alternative geographic boundaries for organ allocation. For example, current allocation rules require that adolescent donor lungs be allocated locally first to adolescents, then to children and then to adults. In a recent study published in the *American Journal of Transplantation*, we showed that if the same adolescent donor lungs are offered more broadly first to wait-listed children and then adolescents within a 1,000-mile radius before local wait-listed adults are considered, both the child and adolescent transplant rates will potentially increase without adversely impacting the adult transplant rates.

The simulation models and their results, which were developed by the Scientific Registry of Transplant Recipients for the Organ Procurement and Transplantation Network (OPTN), the government organization charged with establishing and maintaining U.S. transplant policy, are under review as possible alternatives to the current U.S. lung allocation policy.

In addition to this project, we are engaged in ongoing research to define the impact of expansion of recipient and donor selection criteria on lung transplant outcomes, and alternative lung allocation models to improve patient access, outcomes and quality of life. ●

Dr. Tsuang is is a member of the Lung Transplantation section and Department of Critical Care Medicine. He can be reached at 216.445.6448 or tsuangw@ccf.org.

Dr. Valapour is Director of Lung Transplant Outcomes at the Respiratory Institute. She can be reached at 216.445.4071 or valapom@ccf.org.

References

1. Valapour M, Skeans MA, Heubner BM, et al. OPTN/SRTR 2013 Annual Data Report: lung. *Am J Transplant.* 2015;15(Suppl 2):1-28.

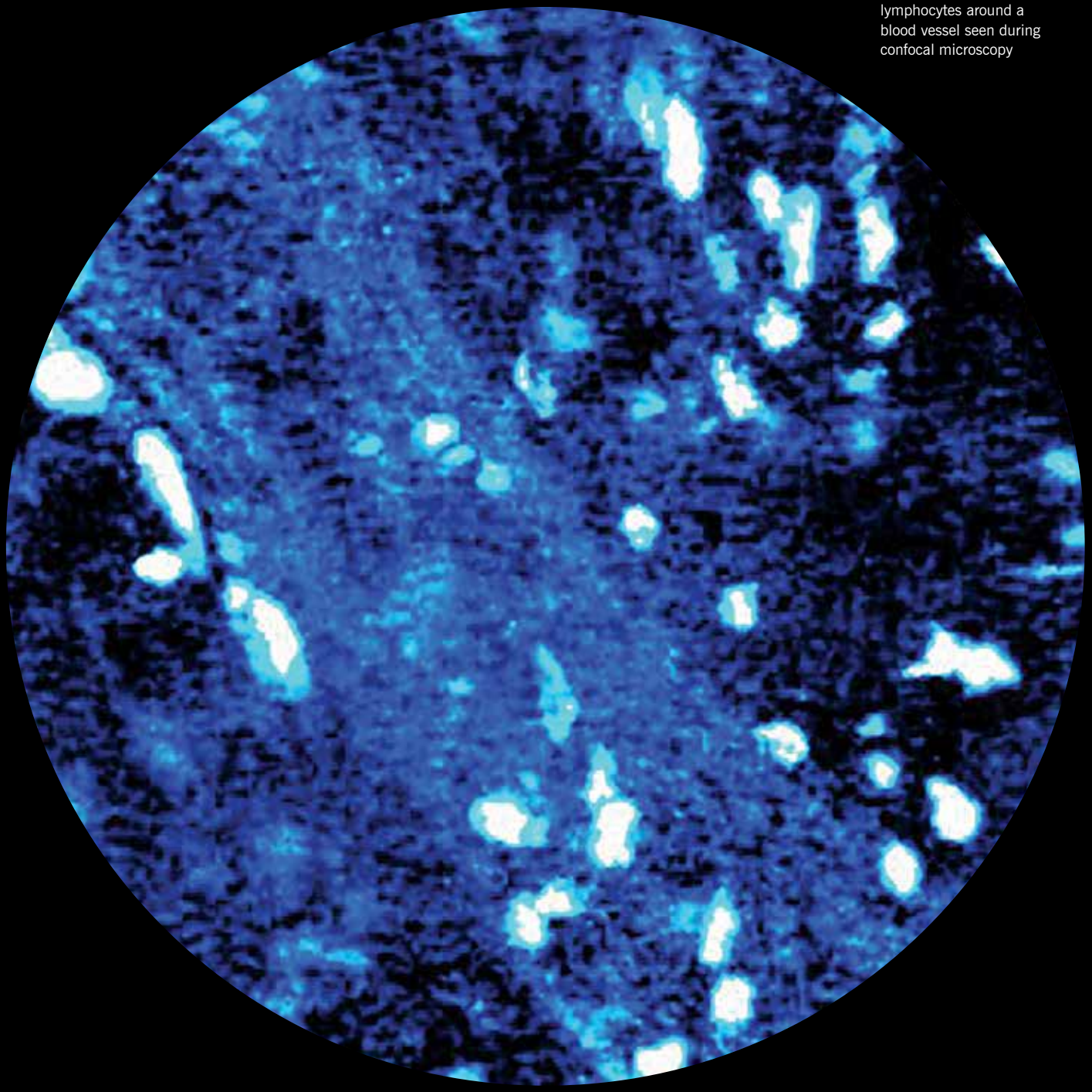
2. Colvin-Adams M, Valapour M, Hertz M, et al. Lung and heart allocation in the United States. *Am J Transplant*. 2012;12(12):3213-3234.

3. Tsuang WM, Chan KM, Skeans MA, Pyke J, Hertz MI, Israni AJ, Robbins-Callahan L, Visner G, Wang X, Wozniak TC, Valapour M. Broader Geographic Sharing of Pediatric Donor Lungs Improves Pediatric Access to Transplant. *Am J Transplant*. 2015 Nov 2. doi: 10.1111/ajt.13507. [Epub ahead of print]

Probe-Based Confocal Light Endomicroscopy and the Optical Biopsy

Optical biopsy eliminates traditional biopsy risks

By Sonali Sethi, MD, Joseph Cicenia, MD, and Marie Budev, DO, MPH



› **Figure 1.** Cluster of lymphocytes around a blood vessel seen during confocal microscopy

Transbronchial biopsy is one of the most important, albeit risky, medical procedures performed after lung transplantation. It is the least invasive way to assess for acute cellular rejection of the lung allograft but is accompanied by the risk of pneumothorax and bleeding. The consequences of these complications can be particularly severe in single-lung transplant recipients since the remaining native lung may not provide sufficient reserve to maintain the patient if the allograft is compromised.

AN EVOLVING DIAGNOSTIC OPTION

Probe-based confocal light endomicroscopy (pCLE) is an evolving technique that permits acquisition of real-time microscopic images of the lung parenchyma at an alveolar level. Based on preliminary studies regarding the utility of this new technology, Cleveland Clinic's lung transplant and bronchoscopy teams are collaborating to determine whether optical biopsies using pCLE can be used to diagnose acute cellular rejection, ideally obviating the need for transbronchial biopsies in this high-risk patient group.

Probe-based confocal light endomicroscopy (pCLE) is an evolving technique that permits acquisition of real-time microscopic images of the lung parenchyma at an alveolar level.

HOW IT WORKS

pCLE is based on the principle of illuminating tissue with a low-power laser and then detecting fluorescent light reflected from the tissue. Using confocal principles, the laser is focused at a specific depth; the light reflected back from that plane is refocused and able to pass through the pinhole confocal aperture, which minimizes scattered light from above and below the plane of interest, increasing spatial resolution. Using inherent autofluorescent properties of tissue, laser scanning can be done at excitatory wavelengths, allowing visualization of target tissue such as elastin, collagen and leukocytes.

pCLE is performed using Mauna Kea Technologies' Cellvizio® system (Mauna Kea Technologies, Paris). Cellvizio is an endomicroscopy system that generates optical biopsies by using a flexible catheter carrying tens of thousands of optical fibers to scan tissue. (Figure 1). The system provides physicians with instantaneous microscopic images of tissue through minimally invasive techniques. Images of the lung parenchyma generated by this system prompted intense interest in applying this technique to a wide variety of pulmonary disorders.

OPTICAL VS. TRADITIONAL BIOPSY

Lung transplant histologic grading is based on guidelines published by the Lung Rejection Study Group in 1990 and revised in 2007. Grading is based exclusively on the location and extent of lymphocytic infiltration around vessels within the lung interstitium. If these patterns can be visualized using pCLE, then it may become possible to use optical biopsies in evaluating for rejection, eliminating the risk of traditional biopsy.

We recently completed enrollment of 200 lung transplant recipients in a prospective study comparing pCLE image acquisition and interpretation with simultaneously obtained transbronchial biopsies in the diagnosis of acute cellular rejection. Data are now being analyzed with the goals of:

1. Identifying image characteristics that correlate with rejection
2. Determining the performance characteristics (e.g., sensitivity, specificity, positive and negative predictive value) of pCLE images in diagnosing rejection
3. Developing a novel grading system of acute rejection based on images rather than histology

ENHANCED CAPABILITIES

We anticipate that the imaging capabilities of pCLE will be further enhanced in the near future with the introduction of specific molecular fluorescent probes that can target particular matrix components (e.g., collagen), cell lines or pathogens (e.g., bacteria). This may not only improve the diagnostic utility of pCLE in the transplant population, but also facilitate wider application of the technique to answer questions related to other pulmonary disorders. ●

Dr. Sethi is a member of the Department of Pulmonary Medicine and can be reached at 216.445.1631 or sethis@ccf.org.

Dr. Cicenia is a member of the Department of Pulmonary Medicine and can be reached at 216.445.8606 or cicenij@ccf.org.

Dr. Budev is the Medical Director of Lung Transplantation and can be reached at 216.444.3194 or budevm@ccf.org

Case Study: Hereditary Hemorrhagic Telangiectasia, Pulmonary Arteriovenous Malformations and Pregnancy

Expert care available at HHT Center of Excellence

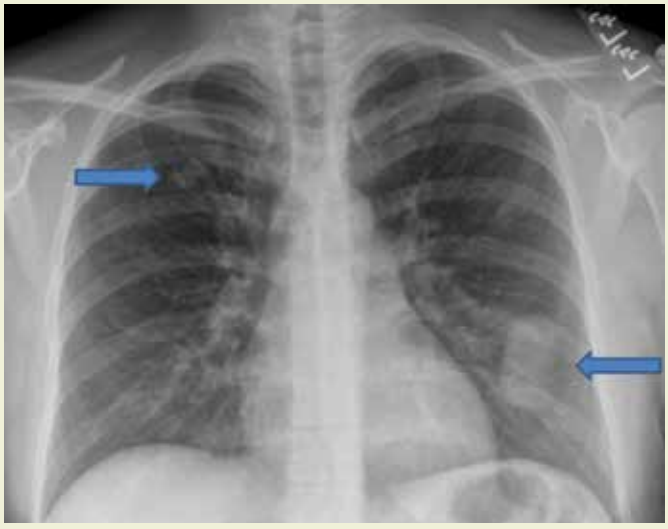
By Joseph G. Parambil, MD, and Charles Martin III, MD

A 30-year-old pregnant female presented for clinical evaluations with a two-week history of pleuritic chest pain. She has a known family history of hereditary hemorrhagic telangiectasia (HHT). Clinical disease was documented in her mother and sister, both of whom had undergone genetic testing that identified a deletion mutation in the endoglin gene (ENG). However, she was never screened for the disease and was asymptomatic until she became pregnant.

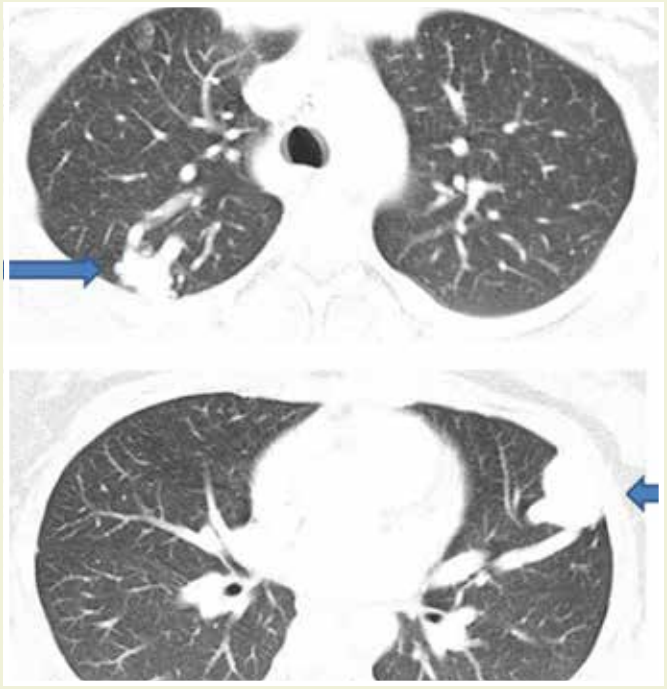
PRESENTATION

With the pregnancy, she began to experience mild episodes of spontaneous epistaxis and also noted the development of cutaneous telangiectasias on her fingertips, lips and chest. As she entered her second trimester, she noticed the onset of exertional dyspnea but attributed this to her gravid uterus. Dyspnea gradually worsened over the subsequent weeks, and two weeks prior to her visit she noted onset of bilateral pleuritic chest pain.

Her obstetrician ordered a chest radiograph that showed bilateral nodular densities (Figure 1). This prompted performance of a chest CT, which demonstrated a 2-cm arteriovenous malformation (AVM) in the right upper lobe and a 4-cm AVM in the lingula (Figures 2 and 3), both of which were abutting the pleura, in addition to multiple smaller AVMs in both lungs.



› **Figure 1:** Chest radiograph shows nonspecific bilateral pulmonary densities, one in the lingula that is ovoid and measures 4 cm x 3 cm, and another in the right upper lobe that is lobulated and measures 2 cm x 1 cm.



› **Figure 2:** Chest CT with contrast shows the mass in the lingula demonstrates a feeding vessel and draining vein consistent with an arteriovenous malformation (AVM) and measures approximately 4.1 cm x 2.3 cm. The lobulated density in the right upper lobe demonstrates feeding vessels as well and represents an AVM measuring 1.7 cm x 1.7 cm.

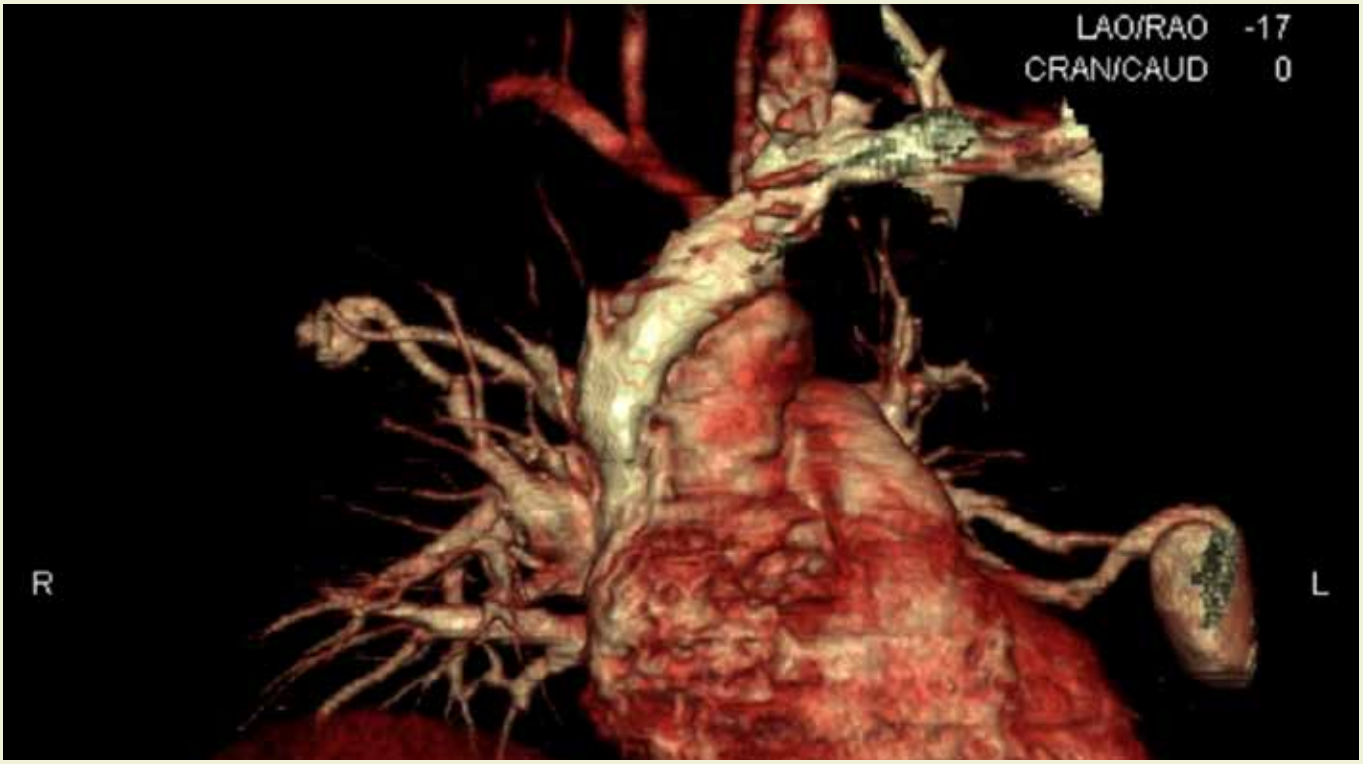
CLEVELAND CLINIC HHT CENTER

She was referred to Cleveland Clinic's HHT Treatment Center where, based on her progressive symptoms and the size of the dominant AVMs, she was admitted to the hospital for consideration of urgent coil embolotherapy.

During her hospital stay, she was assessed by Maternal-Fetal Medicine experts, who confirmed the presence of an appropriate-for-gestational-age baby boy. She underwent genetic testing and was found to have the same ENG mutation as her mother and sister.

TREATMENT

Interventional radiology was consulted for coil embolotherapy. Since she was 26 weeks pregnant, the radiation physicist was consulted to calculate the estimated radiation dose to the developing fetus. To minimize radiation during the procedure, low-dose



› **Figure 3:** Digital reconstruction pulmonary angiogram demonstrating the two AVMs with their associated feeding vessels.

fluoroscopy and abdominal shielding were employed during the procedure and, using ultrasound guidance, the intestines were manually interposed between the diaphragm and the gravid uterus to absorb further radiation scatter from the chest.

The two dominant AVMs were successfully coiled. She tolerated the procedure well without any complications, and her symptoms dissipated the next day. She was discharged home and 14 weeks later delivered a healthy baby boy, who subsequently underwent genetic testing and was found to be negative for the ENG mutation. After delivery, her epistaxis resolved and many of the cutaneous telangiectasias spontaneously regressed.

FOLLOW-UP

Two months after delivery she underwent repeat CT imaging of her chest that showed reduction but persistence of the dominant AVMs in her lungs that now measured 2 cm in the lingula and 1 cm in the right upper lobe. She underwent completion coil embolotherapy to these lesions with no residual flow seen on angiography. Screening MRI of the brain showed no vascular malformations.

A CASE FOR SCREENING

This case highlights the unique risks that pregnancy poses to the patient with HHT. Growth of pulmonary AVMs is likely due to pregnancy-related increase in cardiac output and intravascular volume and/or hormone-induced changes in PAVM wall stability.

It also highlights the importance of clinical screening driven by genetic testing in asymptomatic young relatives of patients with HHT. Due to the age-related penetrance of HHT, there is risk of missing a clinical diagnosis in children and young adults, who might have no epistaxis or visible telangiectasias and yet have HHT and harbor silent, life-threatening pulmonary or cerebral AVMs, as seen in this case.

Care of these complex patients requires specific expertise and a coordinated, multidisciplinary approach, as provided by Cleveland Clinic's HHT Foundation International-designated Center of Excellence. ●

Dr. Parambil is in the Department of Pulmonary Medicine and can be reached at 216.444.7567 or parambj@ccf.org.

Dr. Martin, of Diagnostic Radiology, can be reached at 216.445.5482 or martinc7@ccf.org.

Chronic Thromboembolic Pulmonary Hypertension Program

Experts provide low operative mortality, excellent outcomes

By Gustavo Heresi, MD, and Nicholas Smedira, MD

Pulmonary hypertension due to unresolved pulmonary emboli that narrow elastic pulmonary arteries is known as chronic thromboembolic pulmonary hypertension (CTEPH). This condition is frequently missed as the etiology of dyspnea on exertion or pulmonary hypertension. However, CTEPH is particularly important to diagnose, as it is the only form of pulmonary hypertension that can be potentially cured with a complex surgical procedure called pulmonary thromboendarterectomy (PTE, also known as pulmonary endarterectomy or PEA).

SCREENING FOR CTEPH

The incidence of CTEPH after an acute pulmonary embolism has been reported to be as low as 0.57 percent and as high as 8.8 percent. One of the most cited studies reported an incidence of 3.8 percent within two years. This translates as one patient developing CTEPH out of every 25 who survive an acute pulmonary embolism. A known thrombophilic condition is observed in only a minority of patients, usually antiphospholipid syndrome.

Furthermore, 25 to 50 percent of patients with CTEPH do not have a history of previous pulmonary embolism. Thus, we recommend that all patients with persistent dyspnea after an acute pulmonary embolism, as well as those with pulmonary hypertension of unclear etiology, be evaluated for CTEPH.

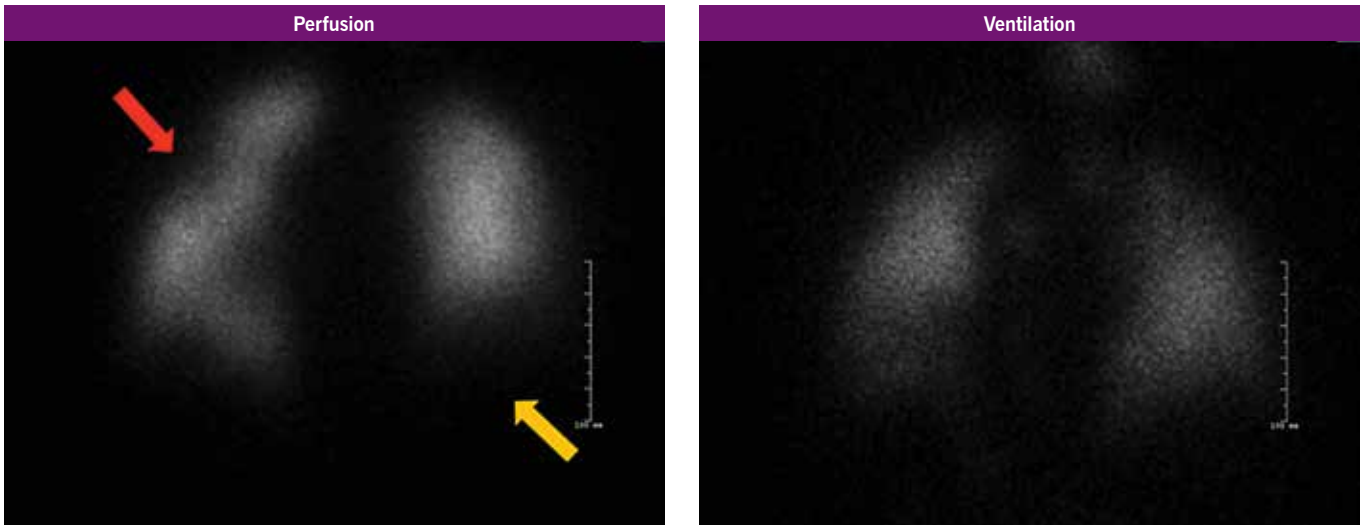
SCREENING OPTIONS

The screening test of choice is the ventilation/perfusion (VQ) scan, as it has the highest sensitivity for the diagnosis of CTEPH. A normal VQ scan excludes this diagnosis. An abnormal result, usually one or more mismatched segmental or larger perfusion defects (Figure 1), should prompt further evaluation. While advances in CT pulmonary angiography have increased its ability to detect CTEPH, the VQ scan is preferred, given the simplicity of the VQ's interpretation, and the difficulty in recognizing chronic thromboembolic lesions on CT.

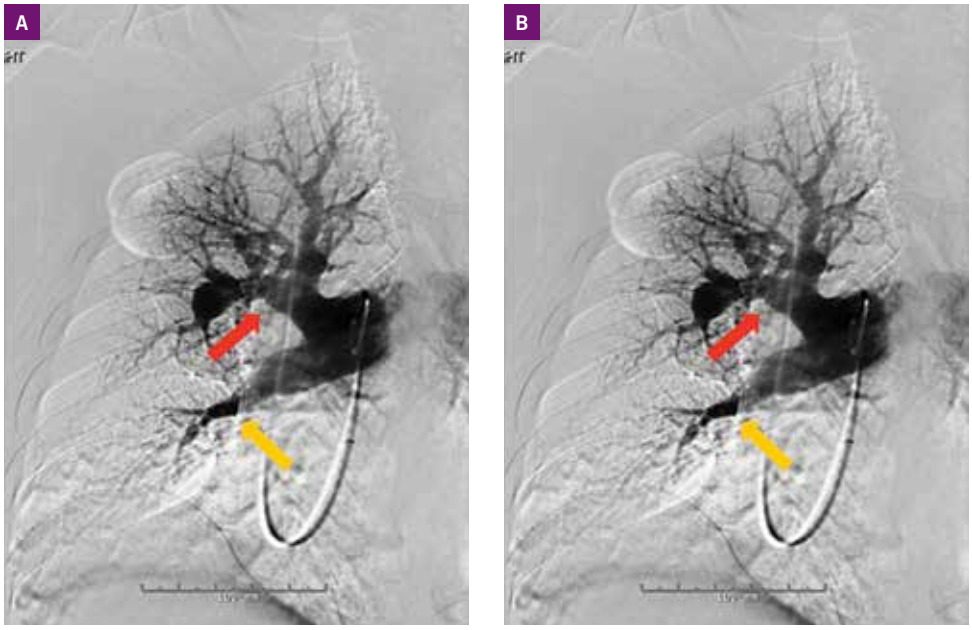
Conventional digital subtraction pulmonary angiography remains the gold standard for CTEPH confirmation and operative planning (Figure 2). Once a diagnosis of CTEPH is established, an assessment of operability is the next step, as PTE surgery offers the potential for cure (Figure 3).

TREATMENT OPTIONS

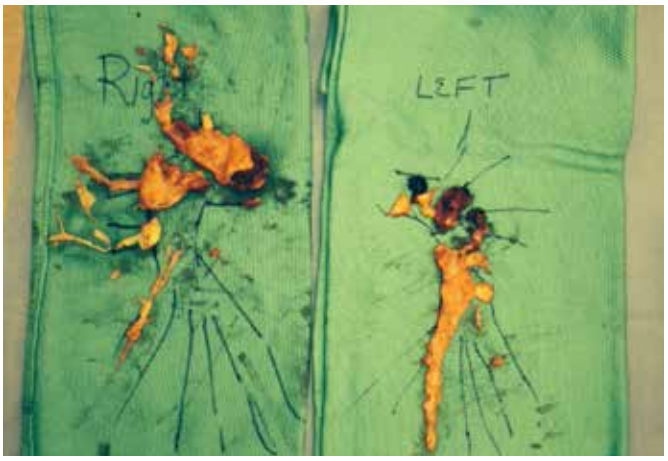
Operability assessment is complex and highly dependent on the experience and expertise of the CTEPH team. Factors that are considered include the thrombotic burden, the degree of hemodynamic compromise and the patient's comorbidities. Pulmonary hypertension-targeted medical therapy is only indicated for patients considered not to be surgical candidates.



› **Figure 1:** Posterior view of a ventilation/perfusion scan of a 54-year-old man with CTEPH. Yellow arrow points at mismatched perfusion defects in the anterior, lateral and posterior basal segments of the right lower lobe. Red arrow points at a mismatched perfusion defect in the posterior portion of the apicoposterior segment of the left upper lobe.



› **Figure 2:** Digital subtraction angiography of the same patient. Panel A: frontal view of the right lung, showing severe stenosis of the descending branch of the pulmonary artery (yellow arrow) with marked hypoperfusion of the right lower lobe, as well as narrowing of the anterior segment of the right upper lobe artery (red arrow) with post-stenotic dilation. Panel B: oblique view of the left lung showing complete stenosis of the posterior segment of the left upper lobe (red arrow) as well as severe irregularities of the basilar segments (yellow arrow).



› **Figure 3:** PTE surgical specimen from the same patient. Preoperative mean pulmonary artery pressure was 60 mm Hg, and it decreased to 24 mm Hg after the operation.

MULTISPECIALTY TEAM

Cleveland Clinic has a multidisciplinary team dedicated to the evaluation and treatment of CTEPH patients. The CTEPH program team includes clinicians specializing in pulmonary medicine, cardiothoracic surgery, nuclear medicine, chest radiology, interventional radiology, cardiovascular medicine, and anesthesiology. Our team is evaluating the role of novel imaging techniques, such as single photon emission computed tomography VQ scintigraphy and dual-energy CT scan (Figure 4), which allow for the assessment of pulmonary perfusion, and emerging therapeutic options such as balloon pulmonary angioplasty.

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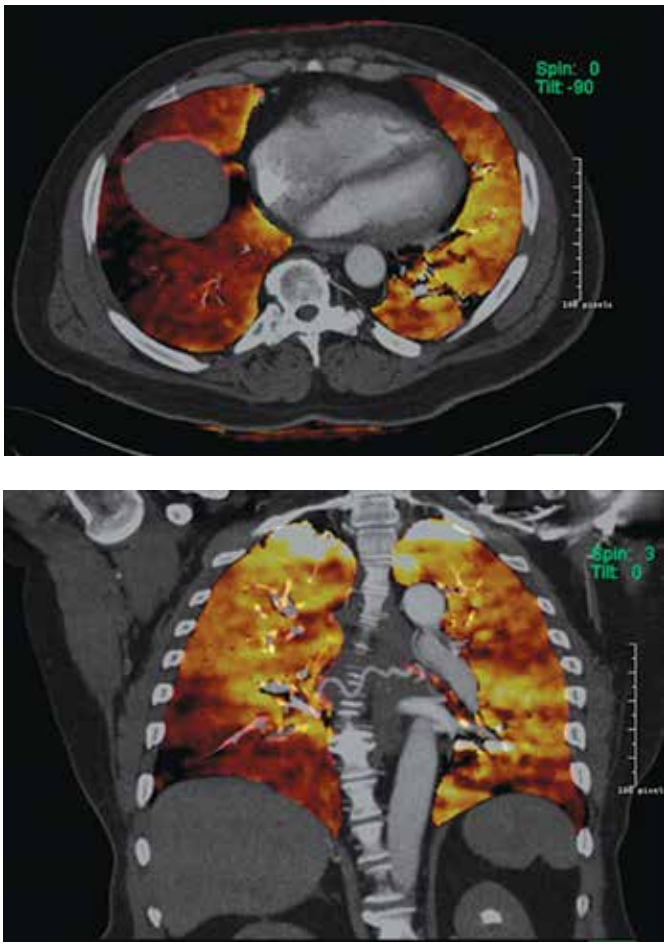
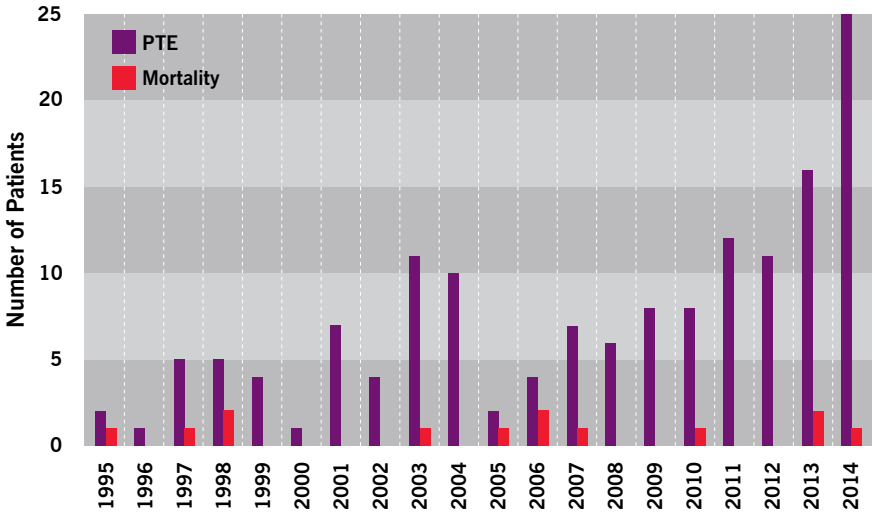


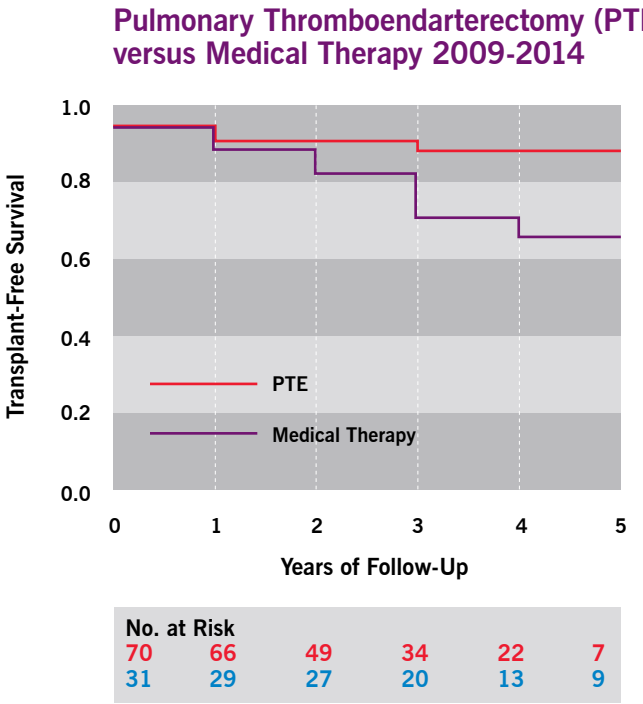
› **Figure 4:** Dual-energy CT of the chest of the same patient. Axial and coronal views. Iodine perfusion maps show decreased perfusion to the right lower lobe. The coronal view also shows bronchial artery hypertrophy, a frequent finding in CTEPH patients.

Hemodynamics Before and After PTE (N = 64) 2011-2014		
	PREOP – Median (25th, 75th percentiles)	**POSTOP** – Median (25th, 75th percentiles)
Mean PAP, mm Hg	45 (39, 55)	25 (22, 31)
CI, L/min/m²	2.2 (1.8, 2.6)	2.9 (2.6, 3.3)
PVR, Wood units	6.2 (4.9, 10.1)	2.4 (1.8, 3.1)

PAP = pulmonary artery pressure, CI = cardiac index, PVR = pulmonary vascular resistance



› **Figure 5:** Pulmonary thromboendarterectomy (PTE) experience (N = 150) 1995-2014



› **Figure 6:** Patients treated with PTE surgery had better survival than those treated with medical therapy (P = 0.04).

PROVEN RESULTS

Over the past 20 years, a total of 150 PTE surgeries have been performed at Cleveland Clinic (Figure 5). Between 1995 and 2010, operative mortality was 11.6 percent. Between 2011 and 2014, volumes doubled and the operative mortality came down to 4.7 percent, a rate comparable to current published literature. With the 2015 surgical volume at the time of writing, in-hospital mortality is down to 3.9 percent.

For the 64 patients who underwent PTE between 2011 and 2014, hemodynamic data show normalization of pulmonary vascular resistance with resultant reduction in pulmonary artery pressure and cardiac index (Table).

Not only are hemodynamic results remarkable and operative mortality low, but long-term outcomes are excellent, with a five-year survival rate of 87.4 percent, compared with 63.3 percent for patients treated with medical therapies (Figure 6). ●

Dr. Heresi, Medical Director of the Pulmonary Thromboendarterectomy Program in the Respiratory Institute, can be reached at 216.636.5327 or heresig@ccf.org.

Dr. Smedira, a cardiothoracic surgeon, can be reached at 216.445.7052 or smedirn@ccf.org.

Case Study: CTEPH and Mediastinal Venous Malformation — Treatment Approach

By Gustavo Heresi, MD; Marcelo Gomes, MD; Karunakaravel Karuppasamy, MD; Abraham Levitin, MD; and Nicholas Smedira, MD

A 21-year-old female with a diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) was referred to Cleveland Clinic for heart-lung transplantation. She was considered not to be a candidate for pulmonary thromboendarterectomy (PTE) due to a large venous malformation in the mediastinum. She was born with a left axillary mass, for which she received no treatment. She reported a one-year history of dyspnea on exertion. Six months prior she had an acute pulmonary embolism. Her dyspnea progressed to functional class III upon presentation in spite of ongoing anticoagulation.

CASE STUDY

Chest computed tomography (CT) showed a huge venous malformation in the left anterior mediastinum lying immediately behind the sternum, extending across the midline anterior to the thoracic aorta and across the thoracic outlet into the left axilla and chest wall (Figure 1A, arrows); the mass abutted the right ventricular outflow tract and the main pulmonary artery (Figure 1B, arrow).

Angiography showed her left axillary vein bifurcated and fed the malformation, which drained into the left innominate and, ultimately, the superior vena cava (SVC). Magnetic resonance angiography additionally depicted thrombosis in the axillary portion of the malformation (Figure 2A, arrows), and a series of tandem covered stents extending 18 cm from the left axillary vein to the SVC (Figure 2B, arrow) that had been placed at another institution to isolate the malformation from the systemic circulation.

Both chest CT (Figure 1B, arrowhead) and invasive pulmonary angiography documented central chronic thromboembolic disease. Right heart catheterization demonstrated severe pulmonary hypertension and severely elevated pulmonary vascular resistance.

TREATMENT PROTOCOL

The patient underwent direct puncture venography of the malformation, which documented minimal early drainage into the mediastinum. Embolization of multiple feeding pathways and of the malformation itself was successfully carried out.

During PTE, the surgeon spent several hours dissecting the mass from the mediastinal structures and mobilizing it both superiorly and to the left side. An incision was made in the thickest portion of the malformation, the clot was extracted and a basket sucker was used to maintain it in a decompressed state.

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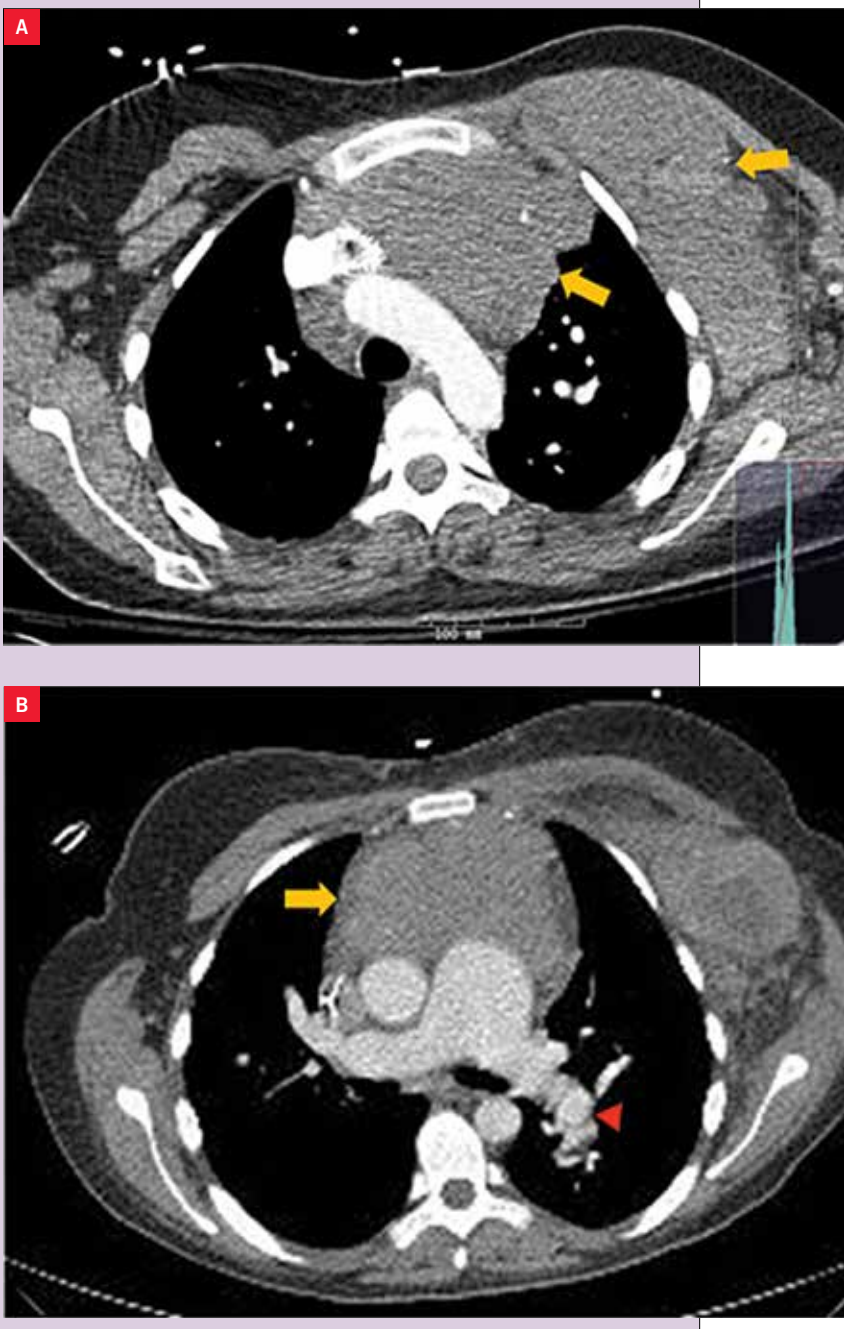
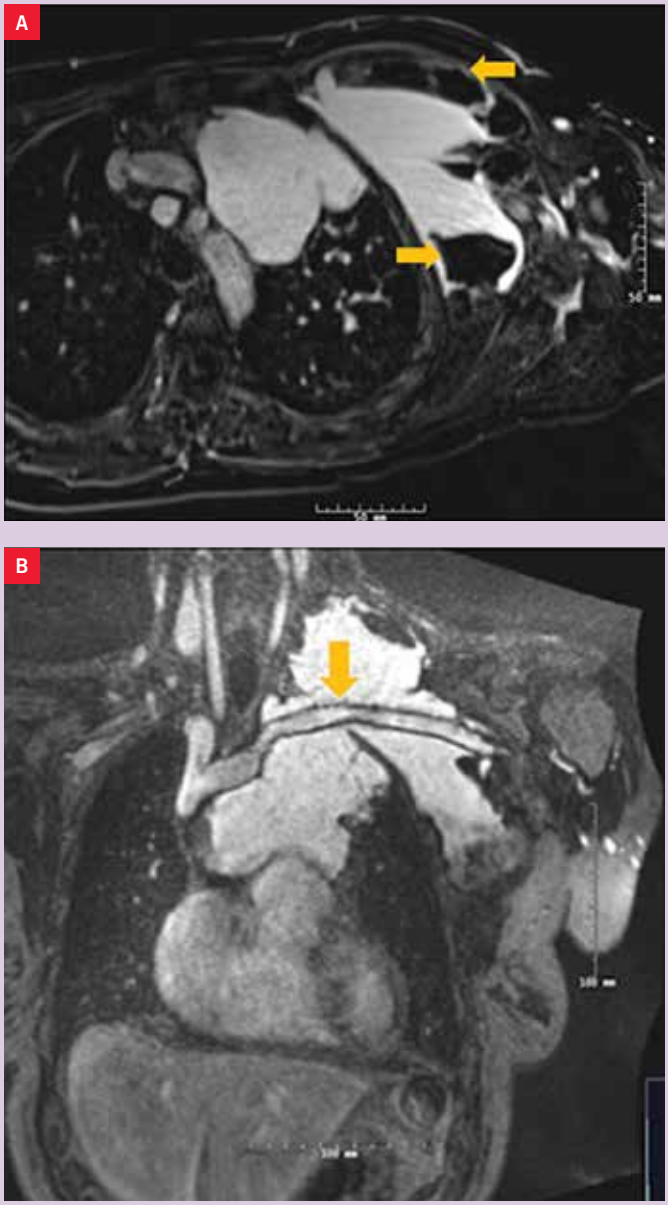


› **Figure 1:** Chest CT documenting central chronic thromboembolic disease.

The estimated five-year survival after PTE is 85 to 90 percent, compared with the estimated 50 percent five-year survival post-lung transplantation.



› **Figure 2:** Magnetic resonance angiography additionally depicted thrombosis in the axillary portion of the malformation (Figure 2A, arrows), and a series of tandem covered stents extending 18 cm from the left axillary vein to the SVC (Figure 2B, arrow) that had been placed at another institution to isolate the malformation from the systemic circulation.

Hemodynamic Improvement

	Pre-PEA	Post-PEA
RAP (mm Hg)	15	11
mPAP (mm Hg)	60	23
PAWP (mm Hg)	7	11
CI (L/min/m^2)	2.3	2.6
PVR (dynes*sec/cm^5)	890	178

A complete endarterectomy was performed using 23 minutes of circulatory arrest for the left and 10 minutes for the right side. The patient had an uneventful postoperative course with significant hemodynamic improvement (Table).

RESULTS

The estimated five-year survival after PTE is 85 to 90 percent, compared with the estimated 50 percent five-year survival post-lung transplantation. Accordingly, performing PTE significantly prolonged the estimated life expectancy of this young woman. ●

Dr. Heresi, Medical Director of the Pulmonary Thromboendarterectomy Program in the Respiratory Institute, can be reached at 216.636.5327 or heresig@ccf.org.

Dr. Gomes, a vascular medicine specialist, can be reached at 216.444.3352 or gomesm2@ccf.org.

Dr. Karuppasamy, an interventional radiologist, can be reached at 216.444.0412 or karuppk@ccf.org.

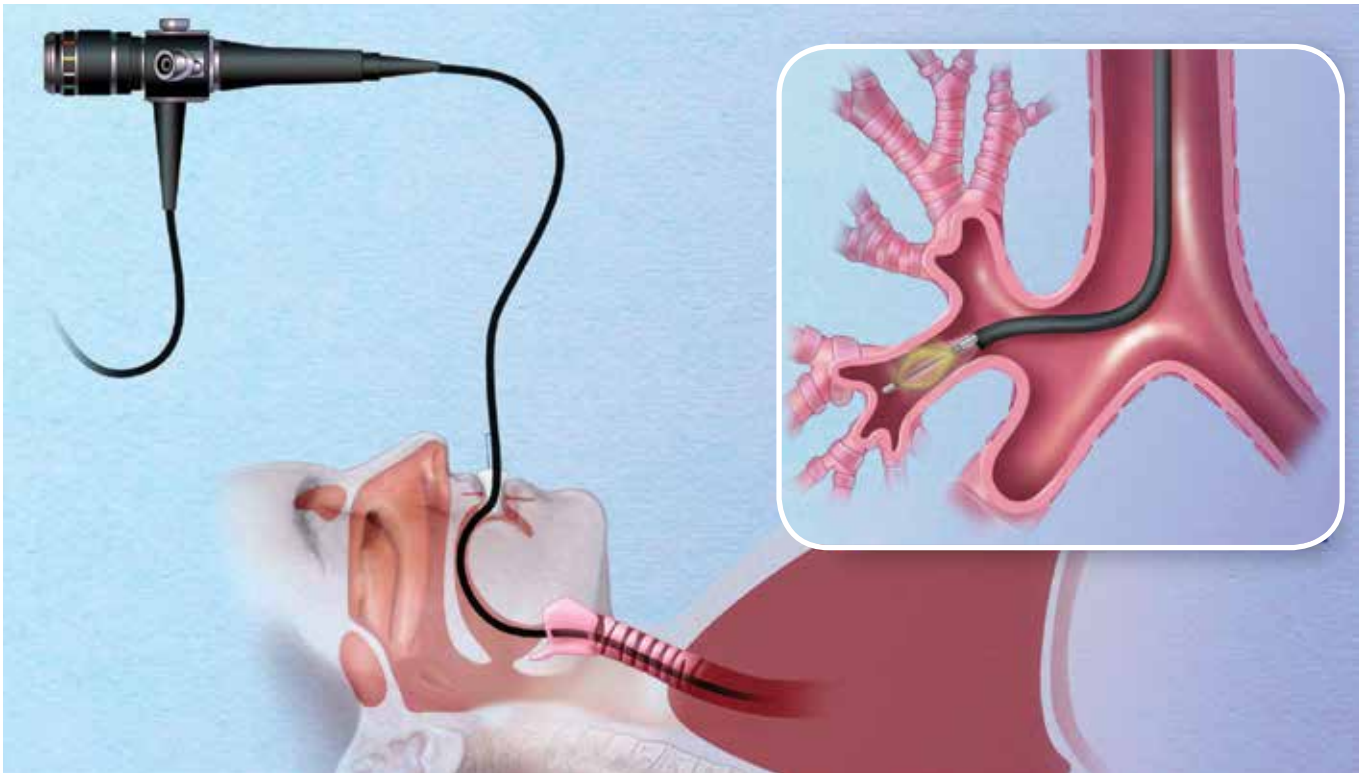
Dr. Levitin, an interventional radiologist, can be reached at 216.444.2244 or levitia@ccf.org.

Dr. Smedira, a cardiothoracic surgeon, can be reached at 216.445.7052 or smedirn@ccf.org.

Cost-Effectiveness of Bronchial Thermoplasty in Severe Uncontrolled Asthma

Patient population, costs determine practicality

By Joe Zein, MD; Sumita Khatri, MD, MS; and Belinda Udeh, PhD, MPH



Bronchial thermoplasty (BT) was approved by the Food and Drug Administration (FDA) in 2010 based on clinical trials demonstrating its effectiveness. Patients with severe persistent asthma are eligible if they are at least 18 years old and their asthma is not well-controlled with inhaled corticosteroids and long-acting beta-agonists. However, the cost-effectiveness of this procedure in treating this patient population remains uncertain.

EXPLORING BT'S COST-EFFECTIVENESS

To further explore this question, we analyzed data using a Markov decision analytic model to estimate the cost effectiveness of BT as compared with usual care. We abstracted our baseline case characteristics from the AIR2 trial (Asthma Intervention Research 2), the only randomized controlled trial published to date.

Although only five-year outcomes data are available from the clinical trial, clinical effectiveness of BT is expected to last beyond five years. We explored the value of BT over a 10-year period after treatment. Further, we assumed the effect of BT remained constant for the first five years, in line with current clinical trial data, and then conservatively estimated that its clinical effect would decrease at a rate of 20 percent for every subsequent year over the next five years. The main outcome measure was cost in 2013 dollars per additional quality adjusted life year (QALY).

We found that treatment with BT resulted in 6.40 QALYs and $7,512 in cost compared with 6.21 QALYs and $2,054 for usual care. The incremental cost-effectiveness ratio (ICER) for BT at 10 years was $29,821/QALY. At five years, BT remained cost-effective with an ICER of $45,300/QALY. At both time points, the cost/QALY fell below the society "willingness to pay" benchmark of $50,000/QALY.

CAVEATS TO AFFORDABILITY

We also conducted sensitivity analysis to assess the combined effect of all uncertainties on the model and to explore the results within the context of population variability. At a society willingness to pay per QALY of $50,000, BT continues to be cost-effective unless the probability of severe asthma exacerbation drops below

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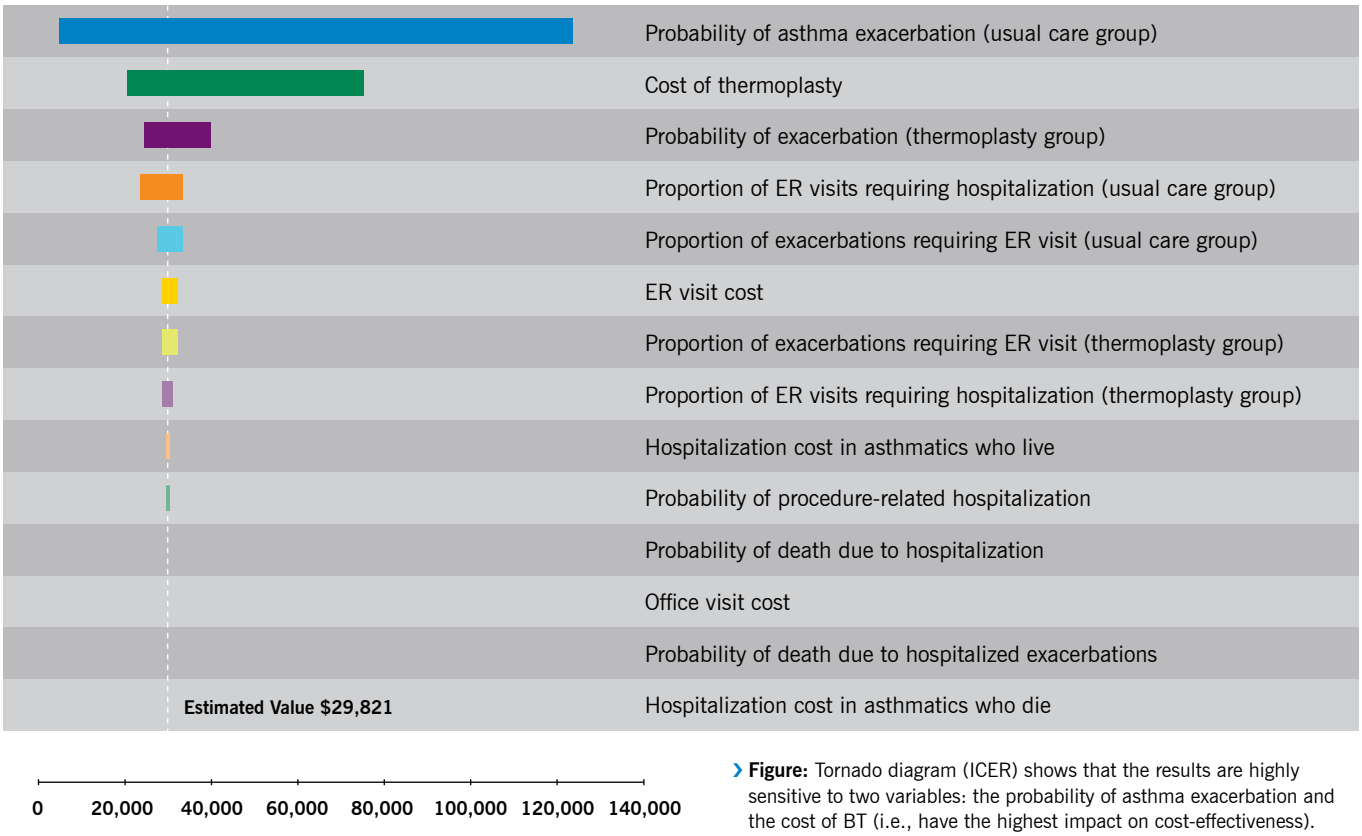

› **Figure:** Tornado diagram (ICER) shows that the results are highly sensitive to two variables: the probability of asthma exacerbation and the cost of BT (i.e., have the highest impact on cost-effectiveness).

Based on our findings, we recommend using BT for younger patients meeting the FDA indication criteria who are at high risk of asthma exacerbation.

0.63 exacerbation per year or the cost of BT rises above $10,384 total for the complete BT treatment (consisting of three separate bronchoscopic procedures).

INDICATIONS FOR BT

Thus, our findings suggest that the cost-effectiveness of BT depends mostly on the probability of asthma exacerbation in the usual care group and on the procedure cost (Figure). To be cost-effective, BT should be used in patients with high asthma exacerbation rates but clinical capacity to safely tolerate BT.

Finally, the cost-effectiveness of BT drops with older patient age due to higher background mortality. Our model population was based on the patient demographics listed in the AIR2 trial with the cohort entering the simulation at age 41, the mean age of the AIR2 trial population. Therefore, the ICER for BT at 10 years of $29,821/QALY cannot be generalized to an older patient population. In that regard, the ICER for BT becomes $157,227 per QALY for individuals who are 65, suggesting that BT may not be cost-effective for older patients with asthma.

Based on our findings, we recommend using BT for younger patients meeting the FDA indication criteria who are at high risk of asthma exacerbation. Continuing to follow beyond five years patients whose severe asthma has been treated with this relatively new procedure will aid the further evaluation of its long-term cost-effectiveness. ●

Dr. Zein, staff in the departments of Pulmonary Medicine and Critical Care Medicine, can be reached at 216.839.3820 or zeinj@ccf.org.

Dr. Khatri, staff in the departments of Pulmonary Medicine and Critical Care Medicine, can be reached at 216.445.1701 or khatris@ccf.org.

Dr. Udeh, a staff health economist, can be reached at 216.445.6214 or udehb@ccf.org.

Adult Cystic Fibrosis and Recent Therapeutic Advances

Game-changing therapies offer dramatic results

By Elliott Dasenbrook, MD, MHS

Cystic fibrosis (CF) is a multisystem, autosomal recessive inherited disease characterized by persistent pulmonary infection, pancreatic insufficiency and elevated sweat chloride levels.[1] While most adult CF patients seen by pulmonologists are diagnosed in childhood, it is estimated that about 5 percent of CF patients are diagnosed after age 18.

NEWLY DIAGNOSED CF

In contrast to pediatric disease, adults newly diagnosed with CF often have milder lung disease, normal pancreatic function, sweat chloride values in the intermediate range and uncommon genetic mutations. It is very important for clinicians to make this diagnosis because despite this "milder" phenotype, adults newly diagnosed with CF are still at risk for subsequent severe lung function decline and decreased survival.

When Dorothy Andersen first comprehensively described CF in 1939, survival was measured in days to months. Over the past 75 years, survival has improved to the point where the current median survival for CF patients in the United States is about 40 years. This tremendous improvement in survival occurred due to an aggressive, multidisciplinary approach to treatment of the nutritional and pulmonary manifestations of CF. We anticipate that survival will continue to increase with the development of therapeutics that treat the basic defect in CF.

TREATING CF'S BASIC GENETIC DEFECT

In 2012, ivacaftor became the first therapy approved by the FDA to treat CF's basic genetic defect. This oral medication is taken twice daily and, to date, has been approved for 10 different CF mutations. These 10 mutations are present in approximately 8 percent of CF patients in the United States, and are seen in CF patients diagnosed in adulthood.

In clinical studies, ivacaftor was associated with significant improvements in lung function, decreased pulmonary exacerbations and change in sweat chloride to the nondiagnostic range.[2] Diagnosing an adult with CF and an ivacaftor-responsive mutation has the potential for a life-altering impact, as illustrated by the following case.

CASE STUDY

A 26-year-old female presented to the clinic with a history of asthma associated with recurrent respiratory tract infections and sinusitis. She had a daily productive cough and frequently missed school and work due to exacerbations. Her gastro-

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intestinal review of systems was normal. Her most recent spirometry revealed a forced expiratory volume in one second (FEV1) of 73 percent of predicted, and there was no response to bronchodilators.

Upon review of a chest radiograph from an ED visit, there was subtle airway dilation and thickening, but only in the upper lobes. Sputum culture and smear for bacteria, fungus and mycobacteria, as well as a computed tomography (CT) exam of the chest, were ordered. The sputum culture grew methicillin-resistant *Staphylococcus aureus* (MRSA). The chest CT revealed upper lobe (right > left) dilated airways with bronchial wall thickening and small-airway mucus plugs in a "tree-in-bud" pattern.

Given these clinical findings, we initiated a diagnostic work-up for upper lobe bronchiectasis with a primary concern for CF. Her immunoglobulin quantitation levels were normal. Sweat chloride measurements were 50 mmol/L and 52 mmol/L, placing her in the "intermediate" range. Sweat chloride levels ≥ 60 mmol/L in this clinical context are considered diagnostic for CF.

Frequently, when the diagnosis of CF is made in adulthood, intermediate sweat results occur and then the next step is to evaluate for CF-related genetic mutations. The patient underwent genetic testing and was found to have F508del (the most common CF mutation) and R117H, a less common variant occasionally seen in patients diagnosed with CF in adulthood. The combination of clinical symptoms suggestive of CF and these two mutations confirmed the diagnosis.

The diagnosis caused significant angst for our patient as her only experience with CF was with a classmate who had died in his teenage years. Through her review of CF on the Internet, she was also aware that MRSA infections in CF are associated with decreased survival and progressive lung function decline.[3-4]

She was very anxious to begin therapy, and the team worked with her on a regimen that included airway clearance, regular exercise, anti-inflammatory therapy and inhaled antibiotics. The results were encouraging with the patient reporting a decrease in the frequency of her pulmonary exacerbations and decreased coughing. Her FEV1 improved to 83 percent of predicted after one year of treatment at the CF center.

GAME-CHANGING THERAPY

After two years of CF therapy directed at the airway obstruction, inflammation and infection, the FDA approved ivacaftor for one of her mutations — the R117H mutation. She began therapy with ivacaftor and there was a dramatic improvement in both subjective and objective measures. She stated that after an initial period of mucus production that was greater than her baseline, her mucus production decreased and it is now rare for her to cough up mucus. In addition, she noticed a significant increase in her exercise tolerance. After six months of ivacaftor therapy, her FEV1 had an absolute increase of 18 percent to 101 percent of predicted, and her chest CT showed resolution of the tree-in-bud pattern in her small airways and no progression of her upper lobe bronchiectasis.

ADULT CYSTIC FIBROSIS PROGRAM

With my recent recruitment to Cleveland Clinic, we established an Adult Cystic Fibrosis Program as part of a comprehensive bronchiectasis center that provides expert diagnosis, leading-edge therapy and research. We set high standards for superior CF respiratory and nutritional outcomes. We partner with our patients to design aggressive management regimens that treat this systemic disease before it results in decline. Therapies that address the basic defect are game changers in the treatment of CF, and we are working toward developing similar therapies for all our CF patients. ●

Dr. Dasenbrook is Director of the Adult Cystic Fibrosis Program and can be reached at 216.445.3082 or dasenbe@ccf.org.

References

1. Dasenbrook EC. Cystic fibrosis and survival in patients with advanced lung disease. *BMJ*. 2011;342:d726.

2. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *TN Engl J Med. 2011;* 365(18):1663-1672.

3. Dasenbrook EC, Checkley W, Merlo CA, Konstan MW, Lechtzin N, Boyle MP. Association between respiratory tract methicillin-resistant Staphylococcus aureus and survival in cystic fibrosis. *JAMA*. 2010;303(23):2386-2392.

4. Dasenbrook EC, Merlo CA, Diener-West M, Lechtzin N, Boyle MP. Persistent methicillin-resistant Staphylococcus aureus and rate of FEV1 decline in cystic fibrosis. *Am J Respir Crit Care Med*. 2008;178(8):814-821.

News Briefs

Sumita Khatri, MD, Co-Director of Cleveland Clinic's Asthma Center, was recognized at the White House in August 2015 by President Barack Obama for her research into the health impacts of climate change. Dr. Khatri was among several researchers recognized during the president's announcement of the Clean Power Plan, which aims to cut carbon pollution from U.S. coal-fired power plants by 32 percent below 2005 levels by 2030. Dr. Khatri is a pulmonary disease specialist in the Department of Pulmonary, Allergy, and Critical Care Medicine. She is a member of the American Thoracic Society and a Fellow in The American College of Chest Physicians. She is co-chair of the Asthma/COPD Assembly of the Healthy Homes Advisory Council in Cuyahoga County and is a member of the national board of directors of the American Lung Association. Her clinical and research interests include the effects of air pollution and environmental triggers on asthma, evaluating biomarkers of asthma, and community engagement with respect to asthma and lung health. She has been involved with the National Institutes of Health-sponsored Severe Asthma Research Program, collaborative research with the U.S. EPA and medical industry-associated asthma therapy trials. ●

Dr. Mehta Receives Endowed Chair

Atul C. Mehta, MBBS, is the inaugural recipient of the Buoncore Family Endowed Chair in Lung Transplantation. The chair is the result of a $2 million gift from Rick and Lori Buoncore to further research in lung transplantation outcomes. Lori Buoncore was diagnosed with interstitial lung disease and was placed on the lung transplant list in August 2014 by Dr. Mehta, a pulmonologist in Cleveland Clinic's Lung Transplant Program. Dr. Mehta performed a successful double lung transplant in November 2014. ●

Cleveland Clinic Repeats as Champion of 2015 CHEST Challenge

For the second year in a row, Cleveland Clinic captured the CHEST Challenge Championship at the American College of Chest Physicians annual meeting in Austin, Texas.

Our team of fellows, including Anupam Kumar, MBBS, Louis Lam, MD, and Sameep Sehgal, MBBS, accumulated 16,561 points in the popular game-show-style challenge to take the top prize in the 14th annual event. Cleveland Clinic Critical Care Medicine Fellowship Training Program Director Rendell Ashton, MD, was presented with a check for $5,000. ●

Respiratory Institute
Selected Clinical Trials

Consider offering your patient enrollment in a leading-edge clinical research trial at our Respiratory Institute. Further information can be obtained by contacting the study coordinator or principal investigator.

SARCOIDOSIS AND INTERSTITIAL LUNG DISEASE

STX-100 in Patients with Idiopathic Pulmonary Fibrosis (IPF)

Sponsored by Stromedix Inc., this randomized, double-blind, placebo-controlled, multiple-dose, dose-escalation study is examining a humanized monoclonal antibody targeting integrin avß6 in IPF patients.

ELIGIBILITY: Patients ages 45-84 years, IPF diagnosis prior to screening via HRCT showing UIP pattern, FVC > 50% of predicted value, DLCO > 30% of predicted value, oxygen saturation > 90% on room air at rest, residual volume ≤ 120% of predicted value, FEV1/FVC ratio 0.65 after use of bronchodilator. Ages 18-44 are eligible if they have a diagnosis of UIP based on surgical lung biopsy.

PRINCIPAL INVESTIGATOR:
Daniel Culver, DO

STUDY COORDINATOR:
Tani Martin, BSN, RN | 216.444.9975

Nicotine Treatment for Pulmonary Sarcoidosis: A Clinical Trial Pilot Study

The objective of this NIH-supported study is to determine if nicotine treatment is safe and efficacious for patients with active pulmonary disease despite conventional therapy.

ELIGIBILITY: Patients 18-75 years old with histologically proven sarcoidosis, evidence of parenchymal disease; evidence of active lung disease based on a 5% change in FVC, TLC or DLCO within the past year; and a Medical Research Council dyspnea score of at least grade 1. Confirmation of active pulmonary sarcoidosis as the cause of worsening pulmonary disease manifestations will be established by the sarcoidosis experts at the site. Patients must be on no treatment or on a stable treatment regimen for sarcoidosis. Exclusion criteria include recent treatment with an anti-TNF-alpha therapy (infliximab, adalimumab, etanercept, etc.), active tobacco smoking or use of smokeless tobacco products containing nicotine, active cardiac or central nervous system disease, history of adverse reaction to nicotine or nicotine-containing products, extensive irreversible pulmonary fibrosis, and inability to provide consent. The patient will be excluded if he or she has a smoking history of greater than 25 pack years, recent (within one year) active smoking or a diagnosis of other significant respiratory disorder other than sarcoidosis that in the opinion of the investigator would complicate the evaluation of response to treatment, or history of substance abuse (drugs or alcohol) within 3 years prior to screening or other circumstances (e.g., psychiatric disease) that could interfere with the subject's adherence to protocol requirements or increase his or her risk of drug (nicotine) dependence. Patients with a diagnosis of current or recently active cancer (within 1 year) will be excluded.

PRINCIPAL INVESTIGATOR:
Daniel Culver, DO

STUDY COORDINATOR:
JoAnne Baran-Smiley, BSN, RN | 216.444.5023

A Double-Blind, Randomized, Placebo-Controlled Trial Evaluating Efficacy and Safety of Oral nintedanib Treatment for at least 52 Weeks in Patients with "Systemic Sclerosis Associated Interstitial Lung Disease" (SSc-ILD)

Sponsored by Boehringer Ingelheim Pharmaceuticals, this is a Phase III trial investigating the efficacy and safety of twice-daily 150 mg nintedanib (vs. placebo) in patients with systemic sclerosis associated interstitial lung disease. The primary endpoint is the annual rate of decline in forced vital capacity (FVC) in mL over 52 weeks.

ELIGIBILITY: Patients ≥ 18 years diagnosed with systemic sclerosis associated interstitial lung disease based on classification according to the most recent ACR/EULAR criteria and HRCT (within previous 12 months); onset of systemic sclerosis (defined as first non-Raynaud symptom) not more than 5 years ago; extent of fibrotic disease in the lung ≥ 10%; FVC ≥ 40% of predicted; DLCO 30% to 89% of predicted (corrected for Hb).

PRINCIPAL INVESTIGATOR:
Kristin Highland, MD, MS

STUDY COORDINATOR:
Ron Wehrmann, RRT | 216.445.0574

FibroGen FGCL-3019-067: Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of FG-3019, a Fully Human, Recombinant DNA-Derived, IgG1 Kappa Monoclonal Antibody that Binds to CTGF in the N-terminal Domain

The primary objective of this study, sponsored by FibroGen Inc., is to determine the effect of FG-3019 on FVC % of predicted in patients with usual interstitial pneumonia (UIP).

ELIGIBILITY: Patients 40-80 years old with < 48 months dx of UIP; FVC 55%-90% of predicted; DLCO > 30% of predicted.

Exclusion criteria include DLCO < 30% of predicted (corrected); FVC > 90% of predicted; evidence of obstructive lung disease by any of the following criteria: RV/TLC < 80%, or RV > 120% of predicted, or extent of emphysema on HRCT greater than the extent of fibrosis on HRCT; treatment with immunosuppressive, cytotoxic or anti-fibrotic drugs (NAC is OK); history of cancer of any type in the 5 years preceding screening visit 1, excluding nonmelanomatous skin cancer, localized bladder cancer or in situ cervical cancer; upper or lower respiratory tract infection of any type within 4 weeks of screening visit 1; planned elective surgery during the study, including 4 weeks following the final dose of study drug; body weight > 130 kg; inadequate IV access; listed for lung transplant.

PRINCIPAL INVESTIGATOR:
Daniel Culver, DO

STUDY COORDINATOR:
Ron Wehrmann, RRT | 216.445.0574

Investigation of the Efficacy of Antimycobacterial Therapy on Pulmonary Sarcoidosis Phase II Randomized, Double-Blind, Placebo-Controlled Trial (CLEAR)

The objective of this NIH-supported study is to assess the efficacy and safety of oral CLEAR therapy in patients with confirmed progressive pulmonary sarcoidosis.

ELIGIBILITY: Selected inclusion criteria include patients with sarcoidosis as defined by the ATS/ERS/WASOG statement on sarcoidosis; biopsy demonstrating granulomas, and no alternative for the cause of the granulomas; evidence of disease progression; positive peripheral immune responses to ESAT-6 as a biomarker of response to the CLEAR regimen; possess evidence of parenchymal or nodal disease on chest radiograph.

PRINCIPAL INVESTIGATOR:
Daniel Culver, DO

STUDY COORDINATOR:
Tani Martin, BSN, RN | 216.445.9557

Ocular Sarcoidosis: Open Label Trial of ACTHAR Gel

Sponsored by Questcor, this study will investigate whether treatment with ACTHAR Gel will result in a reduction of ocular inflammation in patients with active ocular sarcoidosis that requires systemic immunosuppressant therapy.

ELIGIBILITY: Selected inclusion criteria include patients with sarcoidosis as defined by ATS/ERS/WASOG guidelines; any posterior, intermediate or panuveitis of sufficient severity to warrant therapy, in the opinion of the treating physician OR anterior uveitis requiring 4 or more daily applications of topical corticosteroids to maintain control of inflammation, or uncontrolled with topical therapy; persistent disease activity (active uveitis) at the time of screening.

PRINCIPAL INVESTIGATOR:
Daniel Culver, DO

STUDY COORDINATOR:
Tani Martin, BSN, RN | 216.444.9975

ASTHMA

Severe Asthma Research Program (SARP)

Sponsored by the NHLBI, this multicenter, 36-month study is designed to evaluate the pathology of asthma longitudinally.

ELIGIBILITY: Individuals (6-65 years old) who have been clinically diagnosed with asthma and are prescribed oral corticosteroid or high-dose inhaled corticosteroid and long-acting beta agonist or other controller medication. Participants must demonstrate FEV1 bronchodilator reversibility ≥ 12% or airway hyper-responsiveness reflected by a methacholine PC20 ≤ 16 mg/mL. Exclusion criteria include smoking history > 10 pack years if ≥ 30 years of age, or smoking history > 5 pack years if < 30 years of age, and no smoking within the past year.

PRINCIPAL INVESTIGATOR:
Serpil Erzurum, MD

STUDY COORDINATOR:
Marybeth Boyle | 216.445.1756

Alternate Day Diet (ADD)

Sponsored by the NHLBI, this study is looking at the effects of a calorie-restricted diet in asthmatics.

ELIGIBILITY: Participants must be between the ages of 18 and 65 with a diagnosis of asthma. Healthy individuals will also be enrolled for comparison. Exclusion criteria include diabetes (fasting blood sugar > 110 mg/dL), lactose intolerance, BMI > 32 kg/m^2, pregnancy and inability to maintain ADD diet. Low-calorie "shakes" will be provided to participants.

PRINCIPAL INVESTIGATOR:
Serpil Erzurum, MD

STUDY COORDINATOR:
Megan Park | 216.445.1756

A 52-Week, Multicenter, Randomized, Double-Blind, Parallel Group, Placebo Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Tralokinumab in Adults and Adolescents with Asthma Inadequately Controlled on Inhaled Corticosteroid Plus Long-Acting β2-Agonist (STRATOS 1)

Sponsored by AstraZeneca, this study is designed to evaluate efficacy and safety of a fixed 300 mg dose of tralokinumab administered subcutaneously in subjects with uncontrolled asthma on inhaled corticosteroid plus long-acting β2-agonist and having a history of asthma exacerbations.

ELIGIBILITY: Selected inclusion criteria include patients ages 18-75 years, weighing between ≥40 and <150 kg at enrollment; physician-diagnosed asthma for at least 12 months with medium- to high-dose ICS and a LABA; morning pre-BD FEV1 value < 80% at visit 1 and at visit 2 a morning pre-BD FEV1 value of ≥ 40 and < 80%; post-BD reversibility of ≥ 12% and ≥ 200 mL in FEV1; at least 2 documented asthma exacerbations in the 12 months prior to the date that required use of a systemic corticosteroid; ACQ-6 score ≥ 1.5 at visit 1. Selected exclusion criteria include clinically important pulmonary disease other than

asthma; any disorder or major physical impairment that is not stable in the opinion of the investigator; history of anaphylaxis following any biologic therapy or any allergy/reaction to any component of investigation product; tuberculosis requiring treatment within the 12 months prior to enrollment or helminth parasitic infection within 6 months prior to enrollment; current tobacco smoking or a history of tobacco smoking for ≥ 10 pack years; history of cancer or chronic drug or alcohol abuse within 12 months prior to enrollment; use of immunosuppressive medication (including OCS) within 3 months prior to enrollment; receipt of any marketed or investigational biologic agent; current use of five-lipoxygenase inhibitors (e.g., zileuton) or roflumilast; and subjects who have undergone bronchial thermoplasty.

PRINCIPAL INVESTIGATOR:
Sumita Khatri, MD, MS

STUDY COORDINATOR:
JoAnne Baran-Smiley, BSN, RN | 216.444.5023

LUNG CANCER

Lung Cancer Blood and Urine Bank Development

The purpose of this study is to gather blood and urine samples from people who either are at risk of having lung cancer or have been proven to have lung cancer, so that these samples can be used to develop lung cancer tests. The tests developed might be able to predict who will develop lung cancer in the future, or could help doctors diagnose lung cancer. Blood and urine will be collected and stored at -70° C pending worthy projects. Freezer space has been obtained in the lab of Daniel Culver, DO.

ELIGIBILITY: (1) Patients ages 40-90 years, ≥ 10 pack year history; (2) untreated, tissue-confirmed lung cancer, or high suspicion of lung cancer; (3) high risk for lung cancer due to smoking, family history and COPD. Exclusion criteria include any cancers within the past 5 years, any history of lung cancer, immunosuppressive therapy or continuous supplemental oxygen use.

PRINCIPAL INVESTIGATOR:
Peter Mazzone, MD, MPH

STUDY COORDINATOR:
Meredith Seeley | 216.445.9557

Pragmatic Trial of More Versus Less Intensive Strategies for Active Surveillance of Patients With Small Pulmonary Nodules

In conjunction with the Patient Centered Outcomes Research Institute (PCORI) and Kaiser Permanente of California, the main objective of the "Pragmatic trial of more versus less intensive strategies for active surveillance of patients with small pulmonary nodules," also known as the "Lung Nodule Surveillance Trial (LNST)," compares two protocols for lung nodule evaluation, with cluster randomized assignment to treatment groups at the level of the hospital or health system.

The design of the trial is a hospital-based cluster randomized trial of more frequent surveillance versus less frequent surveillance of pulmonary nodules, and immediate or delayed participation in quality improvement collaboratives. Existing medical information systems at each facility will be used to passively enroll patients in the trial. Patients will be enrolled at the time they undergo chest commuted tomography and are found to have a pulmonary nodule of the appropriate size range that meets our inclusion criteria, and who otherwise do not have exclusion criteria (such as no known lung cancer).

PRINCIPAL INVESTIGATOR:
Peter Mazzone, MD, MPH

STUDY COORDINATOR:
Christopher Estling | 216.445.8951

LUNG TRANSPLANT

ECP for the Management of Progressive Bronchiolitis Obliterans Syndrome in Medicare-eligible Recipients of Lung Allografts

The primary aims of this CMS-sponsored prospective cohort registry study are to determine the efficacy and tolerability of ECP for the treatment of progressive BOS after lung transplantation. The study will collect specified demographic, comorbidity, treatment and outcome data exclusively for Medicare beneficiaries treated with ECP for BOS.

ELIGIBILITY: Adult age ≥ 18, Medicare-eligible status, lung transplant recipient (may be combined organ transplant recipients) and strong clinical suspicion for progressive BOS (defined as ongoing decline in FEV1 despite at least one of the following treatments: azithromycin, high-dose steroid, anti-thymocyte globulin, total lymphoid irradiation, sirolimus or everolimus).

PRINCIPAL INVESTIGATOR:
Marie Budev, DO, MPH

STUDY COORDINATOR:
Bette Maierson, BA, RRT | 216.444.2901

A Prospective Multicenter Observational Cohort Study to Define the Risk Factors, Mechanisms and Manifestations of Chronic Lung Allograft Dysfunction (CLAD) Phenotypes-CTOT 20

The primary aim of this NIAID-sponsored noninterventional prospective observational study is to define the risk factors and biological mechanisms that lead to the development of the CLAD phenotypes, BOS and RCLAD, after lung transplantation in order to guide future approaches to prevent or treat CLAD.

ELIGIBILITY: Adult: ≥ 18 years of age; listed for or within 1 month of having received a single or bilateral lung transplant; must be first lung transplant operation.

PRINCIPAL INVESTIGATOR:
Marie Budev, DO, MPH

STUDY COORDINATOR:
Bette Maierson, BA, RRT | 216.444.2901

LUNG VOLUME REDUCTION

Lung Function Improvement After Bronchoscopic Lung Volume Reduction with Pulmonx Endobronchial Valves Used in Treatment of Emphysema (LIBERATE)

Sponsored by Pulmonx, the purpose of this study is to assess the safety and effectiveness of bronchoscopic lung volume reduction (BLVR) using the Pulmonx Endobronchial Valve (EBV) in treated study participants compared with control participants to support a premarket approval application to FDA. One hundred and eighty-three patients who are found to qualify for the study during a bronchoscopy procedure will be randomly assigned to either the study treatment group or the control group. Approximately two-thirds will be randomly assigned to the EBV treatment group and one-third randomly assigned to the control group.

ELIGIBILITY: Completed a supervised pulmonary rehabilitation program < 6 months prior to the baseline exam or is regularly performing maintenance respiratory rehabilitation if initial supervised therapy occurred > 6 months prior; baseline evaluation occurred < 90 days after screening exam; signed written informed consent to participate in study using a form that was reviewed and approved by the IRB; continued nonsmoking between initial screening and baseline exams; FEV1 > 15% or < 45% of predicted value at baseline exam; 6-minute walk distance of < 400 meters at baseline exam.

PRINCIPAL INVESTIGATOR:
Michael Machuzak, MD

STUDY COORDINATOR:
Yvonne Meli, RN | 216.445.4215

PULMONARY HYPERTENSION

Pulmonary Vascular Complications of Liver Disease-2 (PVCLD2)

Sponsored by Perelman School of Medicine at the University of Pennsylvania as a subcontract of the NHLBI, the purpose of this study is to determine if certain genes, hormones or other factors predict the risk of developing lung vessel disease in patients with liver disease and whether they determine outcome.

ELIGIBILITY: Patients age ≥ 18 years with chronic portal hypertension from intrinsic liver disease or portal vein disease, documented by clinical history or liver biopsy, referral for evaluation for liver transplantation (LT) or portopulmonary hypertension (or a known diagnosis of portopulmonary hypertension). Exclusion criteria include having an active infection, active or recent (< 2 weeks) gastrointestinal bleeding, lung transplant or LT recipients, being pregnant.

PRINCIPAL INVESTIGATOR:
Gustavo Heresi, MD

STUDY COORDINATOR:
Kasi Timmerman | 216.444.2140

Pulmonary Arterial Hypertension Treatment with Carvedilol for Heart Failure (PAHTCH)

Sponsored by the NIH, this is a 6-month double-blind, randomized, controlled intervention with three arms preceded by an open-label, 1-week run-in period of the effects of carvedilol in patients with pulmonary arterial hypertension.

ELIGIBILITY: Age 18-65; PAH Class 1 (Dana Point 2008); NYHA/WHO Class I-III; stable on PAH medications for the past 30 days; women of childbearing age must use a double-barrier local contraception until completion of the study.

PRINCIPAL INVESTIGATOR:
Serpil Erzurum, MD

STUDY COORDINATOR:
Didem Uzunaslan, MD | 216.445.7706

RISE-IIP: A Randomized, Double-Blind, Placebo-Controlled Phase II Study to Investigate the Efficacy and Safety of Riociguat (0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg and 2.5 mg TID) in Patients with Symptomatic Pulmonary Hypertension Associated with Idiopathic Interstitial Pneumonias (IIPs)

Sponsored by Bayer HealthCare AG, this study aims to evaluate the safety of treatment with oral riociguat at various doses and the effect on 6-minute walking distance in patients with PH associated with IIP.

ELIGIBILITY: Men and women age 18-80 with a diagnosis of major IIPs or rare IIPs as per ATS/ERS/JRS/ALAT guidelines; FVC ≥ 45%; 6MWD 150-450 meters; diagnosis of PH confirmed by RHC with mPAP ≥ 25 mm Hg, PCWP ≤ 15 mm Hg at rest. Exclusion criteria include acute lung infection or exacerbation, active smoking, reasonable likelihood of receiving lung transplant during the 26-week study period, and PH-specific treatment within 3 months of screening.

PRINCIPAL INVESTIGATOR:
Gustavo Heresi, MD

STUDY COORDINATOR:
Kasi Timmerman | 216.444.2140

A randomized, double-blind, placebo-controlled, prospective, multicenter, parallel group study to assess the safety and efficacy of macitentan in patients with portopulmonary hypertension

Sponsored by Actelion Pharmaceuticals Ltd., this study's main objective is to evaluate the effect of macitentan on pulmonary vascular resistance (PVR) as compared with placebo in patients with portopulmonary hypertension (PoPH).

ELIGIBILITY: Men or women > 18 years with symptomatic PoPH, mPAP > 25 mm Hg, PAWP < 15 mm Hg, PVR > 4 Wood units. Exclusion criteria include severe hepatic impairment, severe obstructive or restrictive lung disease, undergoing dialysis, history of liver transplant, hepatocellular carcinoma, schistosomiasis infection, GI bleeding < 3 months prior to randomization, treatment with ERA within 3 months prior to randomization, treatment with interferon within 3 months prior to randomization, treatment with strong CYP3A4 inhibitors.

PRINCIPAL INVESTIGATOR:
Adriano Tonelli, MD

STUDY COORDINATOR:
Kasi Timmerman | 216.444.2140

International CTEPH Registry

The primary objective is to describe the epidemiology of CTEPH and mode of diagnosis and treatment worldwide and determine long-term outcome as measured by NYHA class and survival.

Sponsored by International CTEPH Association (ICA).

ELIGIBILITY: Patients must be newly diagnosed with CTEPH; have been treated with anticoagulation for at least 3 months before diagnosis of CTEPH; mPAP > = 25 mm Hg at rest, abnormal VQ scan, pulmonary angiogram; CT pulmonary angiogram; or MR pulmonary angiogram confirming chronic thromboembolic disease as recommended by standard guidelines.

PRINCIPAL INVESTIGATOR:
Gustavo Heresi, MD

STUDY COORDINATOR:
Kasi Timmerman | 216.444.2140

U.S. CTEPH REGISTRY

The primary objective is to characterize the demographics, evaluation; and clinical course of WHO Group IV pulmonary hypertension, CTEPH.

Sponsored by University of California, San Diego.

ELIGIBILITY: Must be a permanent resident of the United States; mPAP > 25 at rest and PAWM < 15; radiologic confirmation that chronic thromboembolic disease is the cause of the pulmonary hypertension; one or more mismatched perfusion defect(s) by lung ventilation/perfusion scan and confirmation of chronic thromboembolic disease by evidence of bands/webs, vessel narrowing or occlusion seen on CT pulmonary angiogram (CTA), conventional angiography or R angiography (MRA); patients must be diagnosed with CTEPH within 6 months of being considered for study; patients cannot have an underlying disorder with an anticipated life expectancy of less than 2 years.

PRINCIPAL INVESTIGATOR:
Gustavo Heresi, MD

STUDY COORDINATOR:
Kasi Timmerman | 216.444.2140

CRITICAL CARE MEDICINE

Study of Ganciclovir/Valganciclovir for Prevention of Cytomegalovirus Reactivation in Acute Injury of the Lung and Respiratory Failure (GRAIL)

An NHLBI-supported study to evaluate whether administration of ganciclovir reduces serum IL-6 levels (i.e., reduction between baseline and 14 days post-randomization) in immunocompetent adults with severe sepsis or trauma-associated respiratory failure.

ELIGIBILITY: Selected inclusion criteria include patients age 18 years or older; CMV IgG seropositive; report that patient has previously been tested and found to be CMV seropositive at any time; intubation and requiring mechanical positive pressure ventilation [including acute lung injury/ARDS (EA consensus definition)]; meets criteria for either (a) severe sepsis within a 24-hour time period within the 120-hour window, or (b) trauma with respiratory failure and an ISS score > 15 within a 24-hour time period within the 120-hour window (where mechanical ventilation is not due solely to a head injury).

PRINCIPAL INVESTIGATOR:
R. Duncan Hite, MD

STUDY COORDINATORS:
Michelle Ferrari, BSN, RN | 216.445.1939
Danijela Djureinovic, BSN, RN | 216.445.3960

Re-evaluation Of Systemic Early Neuromuscular Blockade (ROSE)

The objective of this NIH-supported study (PETAL Network) is to assess the efficacy and safety of early neuromuscular blockade in reducing mortality and morbidity in patients with moderate-severe ARDS in comparison with a control group with no routine early neuromuscular blockade.

ELIGIBILITY: Selected inclusion criteria include patients age 18 years or older; endotracheal ventilation for < 5 days (120 hours); presence of all of the following conditions for < 48 hours: PaO2/FiO2 < 150 with PEEP > 8 cm H2O or SpO2/FiO2 ratio that is equivalent to a PaO2/FiO2 < 150 with PEEP > 8 cm, and a confirmatory SpO2/FiO2 ratio 1-6 hours after the initial SpO2/FiO2 ratio determination; bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules; respiratory failure not fully explained by cardiac failure or fluid overload.

PRINCIPAL INVESTIGATOR:
R. Duncan Hite, MD

STUDY COORDINATORS:
Michelle Ferrari, BSN, RN | 216.445.1939
Danijela Djureinovic, BSN, RN | 216.445.3960

Vitamin C Infusion for Treatment in Sepsis-Induced Acute Lung Injury

The objective of this NIH-supported study is to assess the efficacy of a 96-hour intravenous vitamin C infusion protocol (200 mg/kg per 24 hours) in patients with established acute lung injury (ALI) from sepsis.

ELIGIBILITY: Selected inclusion criteria include patients age 18 years or older with a suspected or proven infection, and meeting 2 out of 4 of the criteria for systemic inflammatory response syndrome (SIRS) due to infection, and accompanied by at least 1 criterion for sepsis-induced organ dysfunction (defined as fever > 38ºC (any route) or hypothermia < 36ºC (core temp only); tachycardia heart rate > 90 beats/min or receiving medications that slow heart rate or paced rhythm; leukocytosis (> 12,000 WBC/μL) or leukopenia (< 4,000 WBC/μL or > 10% band forms); respiratory rate > 20 breaths per minute or PaCO2 < 32 or on invasive mechanical ventilation).

PRINCIPAL INVESTIGATOR:
R. Duncan Hite, MD

STUDY COORDINATORS:
Michelle Ferrari, BSN, RN | 216.445.1939
Danijela Djureinovic, BSN, RN | 216.445.3960

A Phase 3, Multicenter, Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Plazomicin Compared with Colistin in Patients with Infection Due to Carbapenem-Resistant Enterobacteriaceae (CRE)

Sponsored by Achaogen Inc., this study is designed to demonstrate the superiority, in terms of all-cause mortality at 28 days, of a plazomicin-based regimen compared with a colistin-based regimen in the treatment of BSI or nosocomial pneumonia due to CRE.

ELIGIBILITY: Selected inclusion criteria include positive blood or lower respiratory tract culture ≤ 72 hours prior to randomization meeting any of the following criteria: direct susceptibility testing on a blood or lower respiratory tract isolate suggesting a carbapenem-resistant member of the Enterobacteriaceae, isolation of a carbapenemase-producing member of the Enterobacteriaceae from blood or lower respiratory tract culture, final susceptibility testing on blood or lower respiratory tract isolate demonstrating a carbapenem-resistant member of the Enterobacteriaceae. Diagnosis of BSI or nosocomial pneumonia in a ventilated patient as follows: all clinical components defining the infection at baseline must have been present within 72 hours: fever (oral or tympanic temperature ≥ 38°C or core body temperature ≥ 38.3°C) or hypothermia (core temperature < 35°C); new-onset arterial hypotension as defined by systolic blood pressure (SBP) < 90 mm Hg, mean arterial pressure (MAP) < 70 or an SBP decrease > 40 mm Hg in the absence of other causes of hypotension; elevated total peripheral white blood cell (WBC) count > 10,000 cells/mm^3, > 15% immature neutrophils (band forms) regardless of total peripheral WBC count, or leukopenia with total WBC count < 4500 cells/mm3.

PRINCIPAL INVESTIGATOR:
Jorge Guzman, MD

STUDY COORDINATORS:
Michelle Ferrari, BSN, RN | 216.445.1939
Danijela Djureinovic, BSN, RN | 216.445.3960

IDIOPATHIC PULMONARY FIBROSIS

An Exploratory Multicenter, Open-Label, Single Arm Study of the Safety And Tolerability of Pirfenidone (Esbriet®) in Combination with Nintedanib (Ofev®) in Patients with Idiopathic Pulmonary Fibrosis

Sponsored by F. Hoffmann-La Roche Ltd., this is an open-label study investigating the safety and tolerability of adding nintedanib to treatment with pirfenidone in patients with idiopathic pulmonary fibrosis (IPF).

ELIGIBILITY: Male or female, age 40 through 80 years old at the start of screening, documented diagnosis of IPF, percent predicted FVC ≥ 50%, percent predicted DLCO (or carbon monoxide transfer capacity converted to DLCO) ≥ 30%. Eligible patients must be receiving chronic treatment with pirfenidone for at least 16 weeks on a stable dose. In patients eligible for this study, nintedanib will be added as an additional treatment for IPF (combination treatment) for 24 weeks. The Primary Safety Objective is the proportion of patients who complete 24 weeks of combination treatment on pirfenidone at a dose of 1602–2403 mg/d and nintedanib at a dose of 200–300 mg/d.

PRINCIPAL INVESTIGATOR:
Joseph Parambil, MD

STUDY COORDINATOR:
Ron Wehrmann, RRT | 216.445.0574

References for Antibiotics Are a Common Cause of Perioperative Anaphylaxis from page 5.

1. Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein D, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol* 2010; 126: 477-522.

2. Hesler BD, Egan C, Besson H, Bauer M, Mascha E, Kurz A, et al. Intraoperative anaphylaxis: a registry analysis. Presented at: the American Society of Anesthesiologists Annual Meeting; October 12-16, 2013, San Francisco, Calif. Poster A3230.

3. Mertes PM, Alla F, Trechot P, Auroy Y, Jougla E, Groupe d'Etudes des Reactions Anaphylactoides Peranesthesiques. Anaphylaxis during anesthesia in France: an 8-year national survey. *J Allergy Clin Immunol* 2011; 128: 366-373.

4. Gonzalez-Estrada A, Pien L, Zell K, Wang X, Lang DM. Antibiotics are an important identifiable cause of perioperative anaphylaxis in the US. *J Allergy Clin Immunol Pract* 2015; 3: 101-5.

5. Gurrieri C, Weingarten TN, Martin DP, Babovic N, Narr BJ, Sprung J, Volcheck GW. Allergic reactions during anesthesia at a large United States referral center. *Anesth Analg* 2011; 113: 1202-12.

5. Guyer AC, Saff RR, Conroy M, Blumenthal KG, Camargo CA Jr, Long AA, et al. Comprehensive allergy evaluation is useful in the subsequent care of patients with drug hypersensitivity reactions during anesthesia. *J Allergy Clin Immunol Pract.* 2015; 3: 94-100

Respiratory Institute **Staff Directory**

Herbert P. Wiedemann, MD, MBA
Chairman, Respiratory Institute
216.444.8335
Specialty Interests: critical care, general pulmonary medicine

Departments of Pulmonary & Critical Care Medicine

R. Duncan Hite, MD
Chairman, Department of Critical Care; Joint Appointment with Pathobiology
216.445.3099
Specialty Interests: critical care, general pulmonary medicine

Robert Kotloff, MD
Chairman, Department of Pulmonary Medicine
216.445.9460
Specialty Interests: general pulmonary medicine, lung transplantation

Loutfi Aboussouan, MD
Joint Appointment with Sleep Center
216.444.0420
Specialty Interests: general pulmonary medicine, neuromuscular diseases, sleep medicine, long-term ventilator care

Muzaffar Ahmad, MD
216.444.6506
Specialty Interests: pulmonary function lab, asthma, lung cancer

Olufemi Akindipe, MD
216.444.0569
Specialty Interest: lung transplantation

Narendrakumar Alappan, MD
216.476.7983
Specialty Interests: critical care, general pulmonary medicine

Francisco Almeida, MD, MS
Director, Interventional Pulmonary Medicine Fellowship Program
216.444.1908
Specialty Interests: advanced diagnostic and interventional bronchoscopy

Rendell Ashton, MD
Associate Director, MICU; Director, Pulmonary and Critical Care Fellowship Program
216.636.5321
Specialty Interests: critical care, medical education, interstitial lung disease

David Berzon, MD
440.312.7140
Specialty Interests: general pulmonary medicine, critical care

Akhil P. Bindra, MD
216.292.5750
Specialty Interests: critical care, general pulmonary medicine

James Blackburn, DO
216.445.7772
Specialty Interest: general pulmonary medicine

Marie Budev, DO, MPH
Medical Director, Lung Transplantation
216.444.3194
Specialty Interests: lung transplantation, pulmonary hypertension, gender-specific pulmonary issues

Ronald Burwinkel, MD
440.312.7140
Specialty Interests: critical care, general pulmonary medicine

Robert Castele, MD
440.878.2500
Specialty Interest: general pulmonary medicine

Jonathon Castro, MD, MS
216.292.5750
Specialty Interests: critical care, general pulmonary medicine

Neal Chaisson, MD
Associate Director, Pulmonary and Critical Care Fellowship Program
216.444.7943
Specialty Interests: critical care, general pulmonary medicine

Humberto Choi, MD
216.444.4875
Specialty Interests: critical care, lung cancer

Chirag Choudhary, MD
Director, MICU, Marymount Hospital
216.444.6090
Specialty Interest: critical care

Joseph Cicenia, MD
216.445.8606
Specialty Interests: advanced diagnostic bronchoscopy, general pulmonary medicine

Stephanie Clough, MD
216.444.6503
Specialty Interests: general pulmonary medicine, critical care

Anthony Cucci, MD
330.344.6676
Specialty Interests: critical care, general pulmonary medicine

Daniel Culver, DO
Director, Sarcoidosis Program; Joint Appointment with Pathobiology
216.444.6508
Specialty Interests: sarcoidosis, interstitial lung disease, hypersensitivity pneumonitis

Elliott Dasenbrook, MD, MHS
Director, Adult Cystic Fibrosis Program
216.445.3082
Specialty Interests: cystic fibrosis, general pulmonary medicine

Abhijit Duggal, MD, MPH
216.444.4838
Specialty Interest: critical care

Jean Louis Dupiton, MD
Director, Hillcrest Hospital ICU
216.444.0751
Specialty Interest: critical care

Amit Diwakar, MD
330.344.6676
Specialty Interests: critical care, general pulmonary medicine

Raed A. Dweik, MD
Director, Pulmonary Vascular Disease Program
Joint Appointment with Pathobiology
216.445.5763
Specialty Interests: asthma, pulmonary hypertension, chronic beryllium disease, critical care, bronchoscopy, nitric oxide in lung physiology and disease, exhaled markers in lung disease

Serpil C. Erzurum, MD
Chair, Department of Pathobiology, Lerner Research Institute; Director, Cleveland Clinic General Clinical Research Center; Co-Director, Asthma Center
216.445.5764
Specialty Interests: asthma, pulmonary vascular disease, respiratory physiology

Andrew Garrow, MD
440.312.9636
Specialty Interests: critical care, sleep medicine

Thomas R. Gildea, MD, MS
Head, Section of Bronchoscopy
216.444.6490
Specialty Interests: interventional bronchology, lung transplantation

Jorge Guzman, MD
Vice President, Regional Hospital Medical Operations
216.445.5765
Specialty Interests: critical care, sepsis, shock

Tarik Hanane, MD
216.445.2747
Specialty Interest: critical care

Umur Hatipoglu, MD
Quality Improvement Officer
Director, COPD Program
216.636.5344
Specialty Interests: asthma, acute respiratory distress syndrome, general (diagnostic) pulmonary medicine, critical care

Gustavo Heresi, MD
Medical Director, Pulmonary Thromboendarterectomy Program
216.636.5327
Specialty Interests: acute respiratory distress syndrome, pulmonary hypertension, sepsis

Kristin Highland, MD, MS
216.445.5429
Specialty Interests: interstitial lung disease, general pulmonary medicine, rheumatology

Lamia Ibrahim, MD
216.445.1701
Specialty Interests: critical care, asthma, general pulmonary medicine

Harish Kakarala, MD
330.344.6676
Specialty Interests: critical care, general pulmonary medicine, sleep medicine

Aanchal Kapoor, MD
Associate Director, Critical Care Medicine Fellowship Program
216.444.4100
Specialty Interest: critical care

Joseph Khabbaza, MD
216.292.5750
Specialty Interests: critical care, general pulmonary medicine

Safdar Khan, MD
Director, Respiratory Institute West Region
330.721.5700
Specialty Interests: critical care, general pulmonary medicine

Sumita Khatri, MD, MS
Co-Director, Asthma Center; Joint Appointment with Pathobiology
216.445.1701
Specialty Interest: asthma

Sudhir Krishnan, MD
216.445.2570
Specialty Interest: critical care

Charles Lane, MD
216.444.0586
Specialty Interests: lung transplantation, critical care

Ann Leano, MD
330.344.6676
Specialty Interests: critical care, general pulmonary medicine

Kar-Ming Lo, MD
216.292.5750
Specialty Interests: critical care, general pulmonary medicine, sleep medicine

Michael Machuzak, MD
Medical Director, Center for Major Airway Diseases
216.444.2718
Specialty Interests: rigid and flexible bronchoscopy, endobronchial ultrasound, laser, electrocautery, stent placement, bronchoscopic lung volume reduction, transtracheal oxygen catheter placement, lung cancer, pleural diseases, COPD

Peter Mazzone, MD, MPH
Director, Lung Cancer Program
216.445.4812
Specialty Interests: lung cancer, critical care, physician education

Glenn Meden, MD
Chief, Division of Pulmonary and Critical Care Medicine at Hillcrest Hospital; Director, Respiratory Institute East Region
440.312.7140
Specialty Interests: general pulmonary medicine, critical care

Reena Mehra, MD, MS
Joint Appointment with Sleep Center
216.444.6967
Specialty Interests: general pulmonary medicine, sleep medicine

Atul C. Mehta, MD
216.444.2911
Specialty Interests: lung transplantation, endobronchial and bronchoscopic procedures and interventions, transtracheal oxygen therapy

Eduardo Mireles-Cabodevila, MD
Director, Critical Care Fellowship Program
216.445.2523
Specialty Interests: critical care, neuromuscular diseases

Ajit Moghekar, MD
216.444.6317
Specialty Interest: critical care

Timothy C. Murray, MD
330.344.6676
Specialty Interests: critical care, general pulmonary medicine, sleep medicine, hyperbaric medicine

Kathrin Nicolacakis, MD
Director, Medical Compliance, Billing and Reimbursement
216.444.0772
Specialty Interest: general pulmonary medicine

Thomas Olbrych, MD
Director, Respiratory Institute South Region
330.721.5700
Specialty Interests: general pulmonary medicine, cystic fibrosis

Mitchell Olman, MD
Joint Appointment with Pathobiology
216.445.6025
Specialty Interest: interstitial lung disease

Beverly V. O'Neill, MD
Vice President, Medical Operations, Euclid Hospital
216.692.7848
Specialty Interests: general pulmonary medicine, long-term ventilator patients

Aman Pande, MD
440.695.4000
Specialty Interests: critical care, general pulmonary medicine

Joseph G. Parambil, MD
Director, Hereditary Hemorrhagic Telangiectasia (HHT) Center
216.444.7567
Specialty Interests: interstitial lung disease, pulmonary hypertension, HHT, general pulmonary medicine

Michael A. Passero, Jr., MD
330.344.6676
Specialty Interests: critical care, general pulmonary medicine, hyperbaric medicine

Bohdan Pichurko, MD
Director, Pulmonary Function Lab
216.445.6789
Specialty Interest: general pulmonary medicine

Hardeep Rai, MD
330.721.5700
Specialty Interests: general pulmonary medicine, critical care

Prabalini Rajendram, MD
216.476.7983
Specialty Interest: critical care

Jennifer Ramsey, MD, MS
Joint Appointment with Palliative Medicine
216.445.8407
Specialty Interest: critical care

Deborah Rathz, MD, PhD
Joint Appointment with Emergency Medicine
216.445.8318
Specialty Interest: critical care

Muhammad Raza, MD
Director, Respiratory Institute West Region
Director, MICU, Fairview Hospital
216.445.9119
Specialty Interests: general pulmonary medicine, critical care

Anita Reddy, MD
216.444.4506
Specialty Interests: critical care, acute lung injury, interstitial lung disease

Debasis Sahoo, MD
216.444.5978
Specialty Interests: general pulmonary medicine, sarcoidosis, interstitial lung disease

Raymond Salomone, MD
216.639.0448
Specialty Interests: critical care, general pulmonary medicine

Madhu Sasidhar, MD
Head, Section of Respiratory Therapy
216.445.1838
Specialty Interests: critical care, general pulmonary medicine

Rachel Scheraga, MD
Joint Appointment with Pathobiology
216.444.4429
Specialty Interests: critical care, general pulmonary medicine

Sonali Sethi, MD
216.445.1631
Specialty Interests: advanced diagnostic and interventional bronchoscopy, lung cancer

David Skirball, MD
440.639.0448
Specialty Interests: critical care, general pulmonary medicine

Brian Southern, MD
216.444.7655
Joint Appointment with Pathobiology
Specialty Interest: interstitial lung disease

Leah Spinner, MD
440.312.7140
Specialty Interests: critical care, general pulmonary medicine

James K. Stoller, MD, MS
Executive Director, Leadership Development; Chairman, Education Institute
216.444.1960
Specialty Interests: clinical epidemiology, alpha 1-antitrypsin deficiency, respiratory therapy

Anu Suri, MD
216.476.7983
Specialty Interests: critical care, general pulmonary medicine

Rachel Taliercio, DO
216.445.1701
Specialty Interests: general pulmonary medicine, asthma

Sanjiv Tewari, MD
Director, Respiratory Institute Akron Region
Chairman, Department of Medicine Akron General Medical Center
330.344.6676
Specialty Interests: critical care, neuro critical care, general pulmonary medicine, sleep medicine, advanced bronchoscopy

Leslie Tolle, MD
216.444.4882
Specialty Interests: critical care, interstitial lung disease, general pulmonary medicine

Adriano Tonelli, MD
216.444.0812
Specialty Interest: pulmonary hypertension

Wayne Tsuang, MD, MHS
216.445.6448
Specialty Interests: critical care, lung transplantation

Jason Turowski, MD
216.445.7098
Specialty Interests: lung transplantation, critical care, cystic fibrosis

Maryam Valapour, MD, MPP
Director, Lung Transplant Outcomes
216.445.4071
Specialty Interest: lung transplantation

Lokesh Venkateshaiah, MD
330.344.6676
Specialty Interests: critical care, general pulmonary medicine

Anil Vijayan, MD
216.476.7983
Specialty Interests: critical care, general pulmonary medicine

Benjamin Young, MD
216.839.3820
Specialty Interests: critical care, lung cancer, general pulmonary medicine

Joe Zein, MD
216.839.3820
Specialty Interests: critical care, general pulmonary medicine

Department of Allergy and Clinical Immunology

David M. Lang, MD
Chairman, Department of Allergy and Clinical Immunology; Director, Allergy Fellowship Program; Co-Director, Asthma Center
216.445.5810
Specialty Interests: asthma, allergic disorders, sinusitis, urticaria, anaphylaxis, drug desensitization, aspirin sensitivity

Sheila Armogida, MD
330.721.5700
Specialty Interests: allergic disorders, asthma

Mark A. Aronica, MD
Joint Appointment with Pathobiology
216.444.6933
Specialty Interests: asthma, allergic disorders

Bela Faltay, MD
330.252.9310
Specialty Interests: allergic disorders, asthma

James Fernandez, MD, PhD
216.445.8573
Specialty Interests: allergic disorders, clinical immunology, immune deficiency

Sandra Hong, MD
440.878.2500
Specialty Interests: allergic disorders, asthma

Fred H. Hsieh, MD
Joint Appointment with Pathobiology
216.444.3504
Specialty Interests: asthma, allergic disorders, mast cell disorders

Lily C. Pien, MD, MHPE
216.444.6933
Specialty Interests: allergic rhinitis, asthma, drug allergies, latex allergy, medical education

Cristine Radojicic, MD
216.444.6933
Specialty Interests: pediatric and adult allergic rhinitis, asthma, sinusitis

Roxana Siles, MD
216.444.6933
Specialty Interests: allergic disorders, asthma

Ahila Subramanian, MD, MPH
216.444.6933
Specialty Interests: allergic disorders, asthma

Li Zuo, MD
440.204.7400
Specialty Interests: allergic disorders, asthma

CLEVELAND CLINIC FLORIDA RESPIRATORY CENTER

Laurence Smolley, MD
Chairman, Cleveland Clinic Florida Pulmonary and Critical Care Medicine
954.659.5000
Specialty Interests: critical care, general pulmonary medicine, sleep medicine

Cleveland Clinic Florida Pulmonary & Critical Care Medicine

Sajive Aleyes, MD
954.659.5000
Specialty Interests: advanced diagnostic bronchoscopy, lung cancer, critical care, general pulmonary medicine

Sam Faradyan, MD
954.659.5000
Specialty Interests: critical care, asthma, general pulmonary medicine

Sam Gurevich, MD
954.659.5000
Specialty Interests: critical care, general pulmonary medicine

Anas Hadeh, MD
954.659.5000
Specialty Interests: critical care, asthma, general pulmonary medicine

Nydia Martinez, MD
954.659.5000
Specialty Interests: critical care, asthma, general pulmonary medicine

Jinesh Mehta, MD
954.659.5000
Specialty Interests: critical care, asthma, general pulmonary medicine

Franck Rahaghi, MD, MHS
954.659.5000
Specialty Interests: critical care, asthma, general pulmonary medicine, pulmonary hypertension

Cleveland Clinic Florida Allergy & Clinical Immunology

Frank Eidelman, MD
Chairman, Cleveland Clinic Florida Medical Specialties Center
Chairman, Cleveland Clinic Florida Allergy and Clinical Immunology
954.659.5813
Specialty Interests: allergic disorders, asthma

Vesselin Dimov, MD
954.659.5813
Specialty Interests: allergic disorders, asthma

PARTNERS IN OTHER DEPARTMENTS

Diagnostic Radiology Section of Thoracic Imaging

Ruffin J. Graham, MD
Head, Section of Thoracic Imaging
216.444.8756
Specialty Interests: pulmonary thromboembolism, lung cancer and thromboembolic disease

Joseph Azok, MD
216.444.0282
Specialty Interest: thoracic imaging

Subha Ghosh, MD
216.444.1014
Specialty Interest: thoracic imaging

Ryo Benson, MD
216.636.5442
Specialty Interest: thoracic imaging

Michael Bolen, MD
216.636.6168
Specialty Interest: thoracic imaging

Omar Lababede, MD
216.444.9014
Specialty Interest: thoracic imaging

Jason Lempel, MD
216.636.2500
Specialty Interest: thoracic imaging

Rahul Renapurkar, MD
216.445.7050
Specialty Interest: thoracic imaging

Barbara Risius, MD
216.444.6422
Specialty Interest: thoracic radiology

Ruchi Yadav, MD
216.445.7050
Specialty Interest: thoracic imaging

Pulmonary Pathology

Carol F. Farver, MD
Director, Pulmonary Pathology
216.445.7695
Specialty Interest: pulmonary pathology

Andrea Arrossi, MD
216.444.9120
Specialty Interests: pathology of interstitial lung disease; pleural and pulmonary tumors

Sanjay Mukhopadhyay, MD
216.444.5893
Specialty Interest: pulmonary pathology

Thoracic and Cardiovascular Surgery

Gösta Pettersson, MD, PhD
Vice Chairman, Thoracic and Cardiovascular Surgery
216.444.2035
Specialty Interests: lung and heart-lung transplantation

Usman Ahmad, MD
216.444.1921
Specialty Interest: thoracic oncology, general thoracic surgery

Douglas Johnston, MD
216.444.5613
Specialty Interest: lung and heart transplantation

Kenneth McCurry, MD
Surgical Director, Lung Transplantation; Joint Appointment with Pathobiology
216.445.9303
Specialty Interests: lung and heart transplantation, ventricular assist devices, heart failure surgery, lung and heart ischemia-reperfusion injury

Nader Moazami, MD
216.444.6708
Specialty Interests: heart surgery, surgical treatment of heart failure, heart transplantation, mechanical heart assist devices

Nicholas G. Smedira, MD
216.445.7052
Specialty Interests: lung and heart-lung transplantation, pulmonary thromboendarterectomy

Edward Soltesz, MD
216.444.5680
Specialty Interests: adult cardiac surgery, heart transplantation and assist devices, minimally invasive cardiac surgery, valve repair and replacement, endovascular aortic surgery

Section of General Thoracic Surgery

Sudish Murthy, MD, PhD
Head, Section of General Thoracic Surgery
216.444.5640
Specialty Interests: esophageal, pulmonary, mediastinal, chest wall and diaphragm surgery; minimally invasive lung volume reduction surgery; lung transplant surgery

Siva Raja, MD, PhD
216.445.6860
Specialty Interests: lung cancer, esophageal cancer

Daniel Raymond, MD
216.636.1623
Specialty Interests: general thoracic surgery, lung cancer

Cleveland Clinic

The Cleveland Clinic Foundation
Respiratory Institute / AC311
9500 Euclid Ave.
Cleveland, OH 44195

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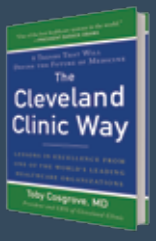

The Cleveland Clinic Way

By Toby Cosgrove, MD, CEO and President, Cleveland Clinic

Great things happen when a medical center puts patients first. Visit clevelandclinic.org/ClevelandClinicWay for details or to order a copy.